INVASIVE CERVICAL CANCER AMONG HIGH-RISK WOMEN: SPATIAL EPIDEMIOLOGY, SCREENING AND ORAL INFECTION

by

Sally Peprah, MSPH

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ABSTRACT

Background

In spite of the general decline in cervical cancer incidence and the highly preventable nature of this cancer, new cases and deaths are recorded annually in Maryland and in other parts of the United States. Using the cancer care continuum and the Human Papillomavirus (HPV) carcinogenesis process as guiding frameworks, this research evaluated the prevention and control of invasive cervical cancer (ICC) among the subgroups at highest risk for disease.

Methods

In Aim 1 using registry data we evaluated space-time variation in ICC incidence over a 10-year period at the county level within the state of Maryland. For Aim 2 we longitudinally assessed utilization and determinants of Pap testing among women living with HIV (WLWH) seen at Johns Hopkins Hospital over a 10-year period. Finally, in Aim 3 using data from HIV positive and high-risk HIV negative women enrolled in the Women's Interagency Health Study (WIHS) cohort, we examined the determinants and risk conferred by prevalent type-specific cervical HPV infections on the acquisition of oral HPV infections.

Results

Aim 1- The overall average annual crude and adjusted state ICC rate between 2003-2012 for Maryland was 7.3 per 100,000. Upon adjusting for contextual differences including median income, age and Pap testing rates at the county level, the average annual adjusted ICC incidence rate in Maryland for this period was 9.2 per 100,000. Within this period,

2003-2012, we identified some clusters with significantly different ICC incidence rates than rates observed in the rest of the state. These included both clusters of significantly lower and higher than expected incidence rates (p-value ≤0.05). Two of the 3 significant clusters of higher than expected ICC incidence rates identified occurred in a more recent time period, 2009-2012. The third significant cluster of high rates was observed in an earlier period, 2005-2008.

Aim 2- Our findings showed that although most WLWH (79%) in clinical care receive Pap testing, some women (21%) are not screened and others (5%) consistently receive Pap testing at intervals longer than recommended. WLWH with a decreased likelihood of screening included older women, injection drug users, white women and those who had lived for a longer time with HIV.

Aim 3- Factors associated with an increased risk of incident oral HPV infection included a recent history of sexual activity with either a male (adjusted hazard (aHR)=2.47, 95%CI: 1.02-6.01) or female partner (aHR=2.79, 95%CI: 1.14, 6.79) as well as a recent history of performing oral sex (aHR=1.75, 95%CI: 1.16, 2.62). No association was observed with type-specific cervical HPV infection, age, alcohol or condom use during oral sex.

Conclusions

Although ICC rates have declined over time, there are still some counties experiencing an anomalously high ICC incidence rate. The recent clusters of high ICC incidence rates identified need to be prioritized and investigated further, while the clusters of low incidence rates identified may represent areas of successful prevention and control within the state of Maryland. The determinants of Pap testing identified in Aim 2 present

potential targets in an urban HIV care setting for closer monitoring and directed interventions to improve Pap test adherence among WLWH. Findings for Aim3 suggest that having a prevalent cervical HPV infection does not increase the risk of an incident type-specific oral HPV infection; however, sexual activity remains a significant risk factor for acquiring oral HPV infections.

ACADEMIC ADVISOR, THESIS AND FINAL EXAM COMMITTEE

Academic Advisor

Gypsyamber D'Souza, PhD, MPH, MS
Associate Professor, Department of Epidemiology

Thesis Committee

Darcy F. Phelan-Emrick, DrPH, MHS
Assistant Scientist, Department of Epidemiology

Anne F. Rositch, PhD, MSPH
Assistant Professor, Department of Epidemiology

Frank C. Curriero, PhD, MA
Associate Professor, Department of Epidemiology

Final Exam Committee

Richard D. Moore, MD MHA
Professor, Department of Medicine

Frank C. Curriero, PhD, MA
Associate Professor, Department of Epidemiology

Joshua M. Sharfstein, MD
Professor, Department of Health Policy and Management

Alternate Examiners

Anne F. Rositch, PhD, MSPH
Assistant Professor, Department of Epidemiology

Jenell S. Coleman, MD, MPH
Associate Professor, Department of Gynecology and Obstetrics

Janice Bowie, PhD, MPH
Professor, Department of Health Behavior and Society

DEDICATION

This dissertation is dedicated to the many women who needlessly develop and die from invasive cervical cancer both here in the United States and around the world; including Mrs. Ernestina Osei, the first woman I saw develop and die from cervical cancer.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

INTRODUCTION

The development and introduction of Pap testing as a secondary prevention tool for invasive cervical cancer (ICC) has led to dramatic declines in national ICC rates over the past few decades [1-3]. In spite of this decline, and a direct annual cost of about $1.55 billion expended on screening alone [4-6], an estimated 12,360 new ICC cases and 4,000 ICC deaths occur annually within the United States. The continued presence of ICC within the United States is said to be largely due to failures across the cancer care continuum, which give rise to missed opportunities for effective prevention and control among the subgroups at highest risk [7-9]. In addition, the burden of ICC is uneven across subgroups within the United States population and the literature identifies racial minorities and middle aged women as being at highest risk for disease [10]. This definition however is not specific; therefore, expanding the current evidence base on the characteristics of the subgroups at highest risk, beyond measures of race and age, may facilitate a more efficient approach to prevention and control among the women most likely to develop ICC.

Presently at the local level epidemiologic data on disease trends and the relevant factors associated with variation in ICC incidence across smaller geographic units is scant [9,11]. In addition, previous examinations of ICC incidence have not assessed the role of contextual factors on any observed variation in disease incidence overtime. This limitation in the available evidence base, in part contributes to the one-size fits all approach to ICC prevention and control that fails to adequately address the needs of the subgroups at highest risk. Thus, identifying the areas with significantly higher or lower

ICC incidence rates, after accounting for contextual differences, will provide additional data for efficient prioritization of ICC needs.

Although routine cervical cancer screening is highly effective and saves lives, over 50% of ICC cases recorded within the United States occur among women who were rarely or never screened for ICC [12-15]. Even when in care, some high-risk women are either never screened or under-screened (i.e. receive no screening or less screening than recommended) for cervical pre-cancers and cancers [16-23]. Included in this group of high-risk women are women living with HIV (WLWH), for whom screening is extremely important given their elevated risk of ICC [24]. However, in the current treatment era, there have been limited longitudinal evaluations of utilization of cervical cancer screening services among WLWH. Cross-sectional studies and relatively short longitudinal evaluations of screening may not adequately reflect screening patterns overtime. Therefore, assessing trends in cervical cancer screening and evaluating potential predictors of utilization using longitudinal follow-up over long periods of time may be a more informative approach to understanding screening among WLWH.

Human Papillomavirus (HPV) is causally linked to both ICC and some oropharyngeal cancers and although sexual behavior greatly influence the risk of HPV infections at the two sites, the association between type-specific infections at the two anatomic sites is not well understood [25]. There are unanswered questions about the potential risk posed by prevalent type-specific cervical HPV infections on the subsequent risk of acquiring the same HPV types orally through autoinoculation. Assessing the relationship between cervical and oral HPV infections will add relevant data to the existing literature on the natural history of oral HPV infections. This is especially important given the relatively

less well understood natural history of oral HPV infections and the recent overall increase in the incidence of HPV associated oropharyngeal cancers [26]. In addition, understanding this relationship might have implications for WLWH, who are known to have a fivefold increased risk of acquiring HPV cervically and are also more susceptible to oral HPV infections.

Research Aims

Given the current challenges outlined above in the prevention of HPV associated malignancies among high-risk women, the overarching purpose of this research is to generate additional evidence to enhance effective prevention and control among the subgroups at highest risk. Specifically, the aims of this research are:

1. **To explore and describe the space-time variation in ICC incidence by county within the state of Maryland from 2003-2012. (Chapter 2)**

   Hypothesis: Although national and Maryland state ICC rates have generally declined, this decrease is not uniform across all counties. Incidence has varied significantly over time and this variation is partly explained by differences in county characteristics including sociodemographic and health care seeking behavior.

2. **To longitudinally describe utilization of Pap testing and assess factors associated with utilization among WLWH enrolled in clinical care at the Moore Clinic of Johns Hopkins Hospital from 2005-2014. (Chapter 3)**

   Hypothesis: Even when enrolled in clinical care, some WLWH do not receive routine Pap testing and others are under-screened. This is associated with clinical and sociodemographic characteristics of WLWH including age, race, type of health insurance and CD4 count.

3. **To assess the determinants and risk conferred by prevalent type-specific cervical HPV infections on the subsequent acquisition of type-specific oral HPV infections. (Chapter 4)**

   Hypothesis: Women with prevalent type-specific cervical HPV infections are at increased risk of acquiring the same HPV types orally.

LITERATURE REVIEW

Cervical Cancer and HPV Infections

ICC is caused by HPV infections, which is the most common sexually transmitted infection within the United States [27,28]. Persistent HPV infections, specifically that of oncogenic subtypes, increase the risk of cervical precancers that often progress to ICC if left untreated [29,30]. Aside ICC, the HPV virus has been etiologically linked to other female cancers including some oropharyngeal cancers, vaginal, vulvar and anal cancers.

Burden of ICC

Compared to other cancers the national burden of ICC is relatively lower and it ranks as the 13th leading cause of cancer cases among females within the United States [31]. Currently the annual incidence rate of ICC in the United States is 7 cases per 100,000 and the mortality rate for ICC is 2 per 100,00 [32,1]. However in spite of the low disease burden, estimates indicate that in 2010 alone about 100, 000 years of life were lost to ICC [33] and by 2020 the total value of lives lost due to cervical cancer will be $13.5 billion [34]. This tremendous cost associated with ICC is largely due to the high disease burden recorded among middle-aged women within the United States. Aside the financial and human cost of disease there are substantial negative societal and familial repercussions

associated with an ICC diagnosis or death and this is especially more pronounced for the subgroups at highest risk of disease.

Disparities In ICC Burden

There are known disparities in ICC incidence and mortality within the United States and some high-risk subgroups have been documented to have an incidence rate as high as 40 per 100,000 population [10]. . This extremely high incidence is about six-times the national average and is similar to rates observed in sub-Saharan Africa, which has the highest burden of ICC globally, with very limited or no formalized ICC prevention and control programs. Thus, the endemic nature and disparate burden of ICC within the US is concerning especially given that ICC is highly preventable and ICC deaths are highly avoidable, at least theoretically, given the availability of effective prevention and treatment strategies.

Beyond Race: Characterizing And Defining Subgroups At Highest Risk

Mainly on account of the high burden among racial minorities, the current literature often characterizes ICC disparities mainly or solely by race. However, race is unlikely to be the sole factor associated with the uneven disease burden across various subgroups within the United States [35]. For example, although white women have the lowest ICC burden nationally, white women living in rural underserved Appalachia have been documented to have incidence rates that are at least 40% higher than the national average [36-38].

Other social and biological factors including health insurance status, level of education, income, competing healthy priorities, comorbidities, geographic location (neighborhood socioeconomic status, degree of urbanization and adjacency to a large metropolitan area) as well as the general health status of women maybe determinants of disease risk and

distribution [39,35]. These other factors are also likely to influence care seeking and utilization. Thus, going beyond race to revise the current definition of the subgroups at highest risk is important as it may potentially enhance the efficiency of current programs in targeting the groups with the greatest ICC needs.

Addressing ICC As A National Public Health Priority

Over the years there have been calls for the expansion of the existing evidence base on the best approaches to address ICC, especially among high-risk groups, with the long-term goal of eliminating this highly preventable cancer from the United States [40,9,41]. One such calls came from the United States Preventive Services Task Force (USPSTF) in 2012, which identified the continued annual recording of ICC cases and deaths within the United States as a public health challenge [9]. The USPSTF listed ICC as one of six high priority areas for targeted action and highlighted the limited scientific evidence on effective strategies for implementing programs among high-risk groups, as a major barrier to effective ICC control [9]. The Task Force specifically stated that in order to further reduce the current burden "more research is needed to understand what factors are associated with inadequate screening and how to help deliver the best screening and treatment" to the subpopulations with the highest disease burden [9].

In addition, the Healthy People 2020 program has listed reducing the number of ICC cases and deaths as one of its cancer specific objectives [40]. The program proposes to assess screening adherence and ICC incidence as a means to promote evidence based screening and to monitor the success of ICC programs [40]. Aside these national programs, some states including Maryland, North and South Carolina, Massachusetts, Alabama, Texas and Utah recognize ICC as a public health priority [42]. These states aim

to eliminate ICC by increasing the proportion of eligible females screened, the proportion appropriately followed-up after a positive screening result and the proportion vaccinated against HPV infections [42].

National ICC Programs

The literature shows that for the general population in care, most of the documented ICC cases occurred among women who were rarely or never screened in the years prior to diagnosis. These reported ICC cases, though having been rarely or never screened for cervical precancers and cancers, did access other health care services on a regular basis in the years prior to diagnosis [12,43]. Hence to address ICC, the Centers For Disease Control supported by an act of Congress, set up the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) in 1990 [44]. The NBCCEDP serves low-income, uninsured, and underserved women by providing access to timely breast and cervical cancer screening and diagnostic services [44]. In addition all states empowered by the Breast and Cervical Cancer Prevention Act, have the discretionary power to offer women diagnosed with precancers or cancer under the NBCCEDP, access to treatment services through state Medicaid programs [44-46].

Even with the NBCCEDP, high-risk groups encounter enormous barriers in accessing services. Overall, less than 90% of those eligible to receive preventive services under NBCCEDP have access to it[47]. While about 60% of women 18-64 years who are eligible under the NBCCEDP, get screened outside of the program and the remaining 33.3% do not receive screening as recommended [47]. Barriers documented to impede access at the national level, for the entire program, include geographic barriers, high cost

of copays, limited health literacy and self-efficacy, competing health and personal priorities as well as suboptimal care provided within the cancer continuum.

ICC Prevention and Control in Maryland

The state of Maryland currently has ICC rates similar to the national average and has outlined objectives within its current cancer control plan to address the disparities that drive ICC persistence [48]. In this plan ICC is specifically listed as one of the cancers for increased policy focus and targeted state action. The state as part of its NBCCEDP offers free cervical cancer screening and treatment services. Yet in spite of this program, ICC is still persistent in Maryland and new ICC cases and deaths are recorded annually. A recent assessment of the quality of ICC treatment received by patients diagnosed in Maryland showed significant differences in the appropriateness and type of care received by racial minority groups within the state [49]. Thus, it is unclear if the current state program is able to identify and deliver interventions to the sub-groups and areas with the greatest ICC burden.

Enhancing The Effectiveness of Current Programs Using Spatial and Temporal Analysis

Currently there is limited available data at the local level within states, on the rates and factors associated with ICC incidence and mortality, especially among high-risk sub-groups [50]. Further, most of the available data and estimates are based on large aerial units such at the state, regional and national levels, which are likely to be heterogeneous in terms of their composition and risk profile of residents. Additionally, the combined effect of contextual factors including socioeconomic characteristics, overall health status, screening rates as well as race and how they might contribute to ICC incidence has not

been extensively assessed. These data limitations in part accounts for the blanket one-size fits all approach to the delivery of ICC interventions [50], where programs often fail to account for underlying differences in risk profiles especially among groups and areas at highest risk.

Spatial epidemiology presents a formal way to separate signal from noise in examinations of trends in incidence across geographic units and over time while accounting for relevant factors that might influence any observed variation [51-54]. Tools from the field of spatial epidemiology, for example a cluster detection approach, allows for the objective identification and visualization of geographic areas of anomalous cancer incidence in space and time [55]. Further; areas of significantly high or low cancer incidence identified using spatial epidemiology can inform efficient redistribution of cancer prevention and control efforts [56,33]. Estimating disease rates at aerial units smaller than the state level (e.g. county or census tract level) might improve the efficiency and effective targeting of the subpopulations at highest risk. This will ensure that the available effective prevention and treatment strategies for ICC are delivered and utilized in the most impactful cost-effective manner.

HIV Patients As A High-Risk Group For ICC

Women living with HIV (WLWH) are at an increased risk of developing ICC and this is as a result of their increased susceptibility to HPV infections and their decreased ability to clear HPV infections once acquired [57]. Among WLWH, ICC is the most prevalent AIDS associated malignancy and an ICC diagnosis is considered as AIDS defining [58]. Compared to the general population, WLWH have an increased risk of developing cervical precancers and cancers [59,60]. In addition, the rate of progression from one

stage of the HPV carcinogenesis process to the next is much faster among WLWH [60,61]. Also for WLWH, ICC treatment failure rates are known to be higher and survival rates are much lower compared to women in the general population [62].

ICC Screening Among WLWH

The subgroups at highest risk of ICC, often have limited access to routine screening and prevention within the cancer care continuum and account for over 60% of all ICC cases [63,7]. By virtue of their increased risk, prior to 2015, it was recommended that WLWH receive cervical cancer screening twice, at six-months intervals, within the first year of diagnosis and if both results were normal, cervical cancer screening could then be administered on a yearly thereafter [64,65]. More recently these guidelines for WLWH have been updated to suggest a three-year follow-up interval among women with 3 consecutive normal Pap test results [66]. Notwithstanding these guidelines, some studies have shown about 25% of HIV positive women in care do not receive cervical cancer screening on a routine basis, as is recommended [61]. However, these previous studies have largely been cross-sectional in nature, relied on self-reports, or followed WLWH in clinical care for a relatively short period of time [16-23]. Therefore, longitudinally evaluating cervical cancer screening and the factors associated with under utilization of screening will provide relevant for improving screening adherence among WLWH.

Autoinoculation As A Mechanism For Acquiring Type-Specific HPV Infections

Although HPV infections are transmitted primarily through sexual contact, there is some potential for transmission through non-penetrative sexual contact through masturbation and infection may also be transmitted through autoinoculation [67,68]. Autoinoculation refers to the “transmission of a prevalent HPV infection between the genitals, anal canal,

oral cavity or hands of an infected individual during routine genital self-handling" [67,69]. Plausibility for autoinoculation is supported by evidence from a cohort of newly sexually active females, where HPV DNA was detected in the fingertips of 30% of women with prevalent cervical infections of at least one HPV type [68]. The concordance rate between types detected in cervical and fingertip samples was 60% and over 90% of these had the same variants detected in both cervical and fingertip samples [68]. Suggesting outside of sexual transmission, transfer of infections between anatomic sites such as the cervix and oropharynx may occur through deposition of HPV DNA on the fingertips of individuals with prevalent infections.

Oral HPV Infections

In the US, 40-80% of oropharyngeal cancers are associated with HPV [70-72]. Oral acquisition and subsequent persistence of some high-risk types elevates the risk of HPV associated oropharyngeal cancers [73,74]. This is especially true for HPV 16 infections, which aside being the main HPV type associated oropharyngeal cancers, has a longer time to oral clearance compared to other high-risk HPV types [25] . For these HPV associated oropharyngeal cancers, HPV 16 is the main oncogenic subtype and is causally linked to about 90% of HPV associated oropharyngeal cancers and 60% of all ICC [70-72]. However, in spite of the common etiologic link between cancers at these two anatomic sites, the relationship between HPV infections at both sites is not well elucidated. Further, unlike cervical HPV infection, the natural history of oral HPV infection is relatively less well understood [25].

Correlation Between Type-Specific Cervical and Oral HPV Infections

A cross-sectional examination of the correlation between prevalent oral and cervical HPV infections, compared to women without a cervical infection, the prevalence of oral HPV infections among women with cervical HPV infections was significantly higher (25.5% versus 7.9% p-value= 0.002) [75]. Further examination of type-specific concordance after correcting for chance agreement, demonstrated 6.3% type concordance between infections at the two anatomic sites [75]. A more recent study using national survey data in the United States, observed a fivefold higher prevalence of oral HPV infections among women with cervical infections when compared to women without a cervical HPV infection [76]. Using data from 10 studies a meta-analysis of correlation by type between cervical and oral HPV infections reported a pooled prevalence of 18.% for oral HPV infections among women with a cervical infection [77]. For this study the type-specific concordance rate between cervical and oral HPV infections was 46.8% and 15.6%, respectively for WLWH and HIV negative women [77].

Although these previous studies suggest an increased risk of oral HPV infection among women with a cervical infection, there are unanswered questions about the relationship between cervical and oral HPV infections. Due to the mainly cross-sectional nature of these previous assessments [78,75,79] the temporal sequence of oral acquisition could not be explored. Further these studies were severely limited in the sample size utilized. Evaluating the relationship between type-specific cervical and oral HPV infections, using data collected prospectively, will add to the current literature on the role played by cervical HPV infections in the natural history of oral HPV infections.

CONCEPTUAL FRAMEWORK

The theoretical framework guiding this research (Figure1) incorporates the HPV carcinogenesis process into a modified cancer care continuum framework, beginning with primary prevention of HPV malignancies and ending with diagnosis/treatment. The framework recognizes that the development of disease outcomes during the carcinogenesis process including the acquisition of HPV infections, its persistence or the development of invasive disease, is influenced by the underlying biology of an individual [6].

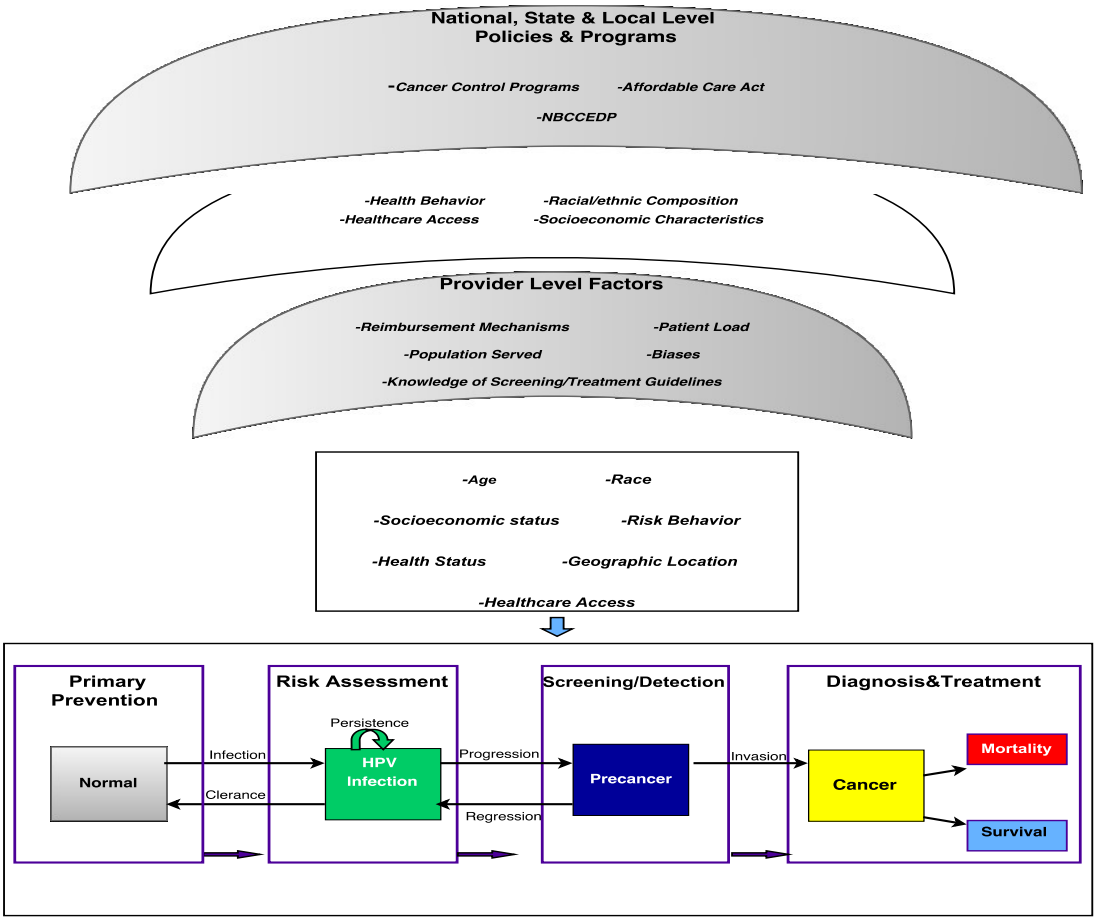

Figure 1-1. Conceptual framework of research study

However, aside this underlying biology, individual patient level factors determine interaction with the care continuum and influence the level of access to cancer care and by extension eventual outcomes with respect to HPV carcinogenesis [8]. Among high-risk individuals level factors that influence interaction with the cancer continuum include age, care-seeking behaviors, socioeconomic status, race and geographic location.

Drawing from the social ecological model, the framework presented above also recognizes that aside individual level factors, factors operating at higher levels might also influence interaction of high-risk patients with the care continuum. These higher level factors include institutional level factors i.e. provider and community level factors as well as national, states and local level policies and programs [80].

Acting either independently or in concert with individual patient characteristics, these higher levels may either directly or indirectly influence the frequency and nature of failures experienced within the cancer care continuum [8]. Therefore, this research seeks to understand the individual level and community level characteristics of high-risk subgroups that promote the development of negative outcomes along the HPV carcinogenesis process. Characterizing these subgroups may potentially improve targeting of available prevention and control efforts and inform the development of appropriate interventions to further accelerate the decline of the current disease burden within the United States.

CHAPTER 2: SPATIAL EPIDEMIOLOGY

A Spatiotemporal Analysis Of Invasive Cervical Cancer Incidence In The State Of Maryland Between 2003-2012

ABSTRACT

Purpose: Invasive cervical cancer (ICC) rates have tremendously declined in the United States, yet new cases consistently occur in Maryland and throughout the United States. We hypothesized that although rates have generally declined, this decline is uneven across counties and over time.

Methods: Using a space-time cluster detection analysis we evaluated clusters of high and low incidence at the county level within the state of Maryland.

Results: The most likely cluster observed was a cluster of low incidence, which included 6 counties in eastern Maryland for the period 2009-2012. A secondary cluster of low rates, comprising 2 metropolitan counties in northern Maryland, was also observed for the period 2009-2012.

Two of the 3 clusters of high ICC rates occurred 2009-2012. This included the large metropolitan area of Baltimore City and another cluster of high rates in Frederick County, in rural western Maryland. The third cluster of high rates was observed 2005-2008, comprising one rural and one metropolitan county in western Maryland.

Conclusion: In recent periods, some counties in Maryland have experienced anomalously high or low ICC incidence. Clusters of high incidence need to be prioritized and investigated, while clusters of low incidence may represent areas of successful prevention and control.

INTRODUCTION

Over the last few decades, rates of invasive cervical cancer (ICC) rates in the United States (US) have steadily declined due to the introduction and use of Pap screening as a screening test for early detection of ICC and its associated precancerous lesions [81,82]. In spite of this decline, 12,360 new ICC cases are diagnosed annually of which about 4,000 go on to die [83] and in 2010 alone about 100, 000 years of life were lost to ICC [33] . The continued presence of ICC in the US is in part due to underlying inequalities and disparities in access to screening and treatment services, which occur as a result of economic and knowledge-related barriers [84,82] that often vary based on the community in which a woman lives. Nationally, there are known disparities in ICC incidence, with racial minorities, low income and rural populations having the highest disease burden [85-90]. For example, ICC incidence rate among older black women is twice the rate among white women of the same age even after accounting for differences in hysterectomy rates [10].

Current ICC incidence in the state of Maryland reflects national rates and similar to national trends, every year there continues to be women diagnosed with ICC and some women dying from ICC in Maryland [49]. Therefore given the availability of effective screening tests and treatment, which makes ICC highly preventable and treatable, the state of Maryland identified ICC as one of its seven high priority cancers for targeted action [91,92]. As part of its ongoing efforts to address ICC, the state offers low-income, uninsured, and underserved women free ICC screening, diagnosis and treatment services through the Centers for Disease Control's National Breast and Cervical Cancer Early

Detection Program (NBCCEDP) [93]. However, even with the NBCCEDP program, prevalence of Pap screening remains lower among some key populations including uninsured women and women without a primary care provider [94]. Further, research in Maryland suggests that compared to white women, black women have significantly higher ICC incidence and mortality rates [91]. In addition, black women are more likely to present with more advanced cases of ICC and are less likely to receive appropriate treatment given the stage of disease [49].

Using a space-time model, a previous examination of variation in ICC incidence by counties in the United States, reported elevated rates in counties with a low prevalence of cervical cancer screening and a higher incidence for some racial minority groups including non-Hispanic blacks, American Indians and Hispanic women [33]. This study however, was conducted for a relative short period (2000-2003) and provided limited information about specific areas of elevated rates. In addition, it did not assess the significance of the observed increase in ICC incidence in some geographic areas, including Maryland.

Indeed previous Maryland state cancer reports have described both overall ICC incidence across Maryland and by counties within the state [91,95]. These reports however, did not examine the space-time variation in ICC incidence across Maryland. Further, previous studies did not assess the combined effect of contextual factors at the county level, (such as socioeconomic characteristics, overall health status, screening rates, and racial composition) and how these factors might influence observed variations in ICC. Hence, this current study assessed variation in ICC incidence by counties in the state of Maryland over a 10-year period. We hypothesized that although national and Maryland

state rates have generally declined overtime, after accounting for differences in relevant county characteristics, some counties have experienced an ICC incidence that is either significantly higher or lower than expected.

METHODS

Data and Study Population

Data on ICC cases diagnosed between January 2003 and December 2012 were obtained from the Maryland Cancer Registry. For each case, data from the Cancer Registry included information on county of residence at diagnosis, age at diagnosis, country and state of birth for those born in the US, marital status, type of reporting source for case diagnosis and/or death, race, grade, metastasis, insurance status and diagnostic confirmation. The analysis was restricted to ICC cases 18 years or older and resident in the state of Maryland at the time of diagnosis. Cases without available information on their county of residence at the time of diagnosis (n=9) were excluded from all county level analyses.

State and county population data as well as racial composition were obtained from the 2010 census and used as denominator for all incidence rate calculations. In addition, annual median household incomes by county were obtained from the Census Bureau's Small Area Income and Population Estimates (https://www.census.gov/did/www/saipe/data/index.html) [96]. Other county characteristics were obtained from the Maryland Behavioral Risk Factor Surveillance System (BRFSS) [97]. For each county, BRFSS data included information on prevalence of obesity and current smoking as well as percentage of females screened for cervical

cancer within the last 3 years. All BRFSS data were obtained biennially (2004, 2006, 2008, 2010 and 2012).

Descriptive Statistics

Characteristics of cases diagnosed within the study period were described using median values and associated interquartile range (IQR) values for continuous variables and percentages for categorical variables. Choropleth maps of average annual crude incidence of ICC by county were developed in ArcGIS [98] for the entire 10-year.

Space-Time Cluster Detection Analyses

Spatial epidemiology presents a formal way to separate signal from noise in examinations of trends in incidence across geographic units and over time while accounting for relevant factors that might influence any observed variation[51-54]. Tools from the field of spatial epidemiology, such as the cluster detection approach, allow for the objective identification and visualization of geographic areas of anomalous cancer incidence in space and time [55]. Further; areas of significantly high or low cancer incidence identified using spatial epidemiology can inform efficient redistribution of cancer prevention and control efforts [56,33].

The study utilized retrospective space-time cluster detection analyses to identify areas of both high and low ICC incidence in Maryland from 2003-2012. The cluster detection analyses were conducted in SaTScan (www.satscan.org) using county of residence at the time of diagnosis, as the geographic unit of aggregation and the initial space-time cluster detection analysis was age adjusted. Adjustments in the SaTScan cluster detection algorithm serves to rule out clusters that would appear solely due to the adjusting variables. Subsequent and final cluster detection analysis were further adjusted for

prevalence of obesity, current smoking, minority (defined as non-white race and/or Hispanic ethnicity), percentage up to date on their cervical cancer screening (measured as Pap test within past 3 years) and median household income within each county.

Given the limited ability of SaTScan to adjust for variables of a continuous nature [99-101], separate Poisson regression analyses for adjusted ICC incidence were performed stratified by year in STATA14 [102] . The fitted or predicted mean of the Poisson regression model represents the expected number of cases per county and year adjusted for the included regression model covariates. These Poisson regression expected counts were imported back into SaTScan for the adjusted cluster detection analyses to search and identify clusters not already explained by the clustering of these adjusting variables.

All cluster detection analyses were conducted using a circular buffer defined from each county centroid location and extending out to only consider clusters (collection of contiguous counties), which combined are within 50% of the total statewide population at risk. In addition, two-year aggregates of time of ICC incidence were utilized to ensure enough statistical power for detecting clusters. Significance of space-time clusters observed to have higher than expected number of ICC was evaluated using Monte Carlo simulations within SaTScan with significance reported as a p-value ≤ 0.05 [99,103,104]. To visualize the results, identified significant clusters were mapped within ArcGIS [98].

RESULTS

There were 2,172 women diagnosed with ICC in Maryland between 2003-2012. At diagnosis, most of the cases (46.7%) were 40-59 years old, with a smaller proportion of women below the age of 30 (4.6%) or 70 years or older (15.8%, Table 2-1). A sizeable proportion of cases were born in the US (42.2%), many of whom were born in Maryland (44.8%, 411/917). Fifty-eight percent of cases were white and 34.5% were black. At diagnosis, most cases had some type of insurance (77.2%), had grade III or IV cancers (28.9%) and no metastasis (64.9%, Table 2-1). Most of the cases were either married or had domestic partners (37.6%) while the remainder were separated or divorced (13.9%), widowed (11.5%) or had never been married (27.2%, Table 2-1).

The average annual crude incidence rate of ICC in Maryland over the 10-year period assessed, was 7.3 per 100,000 and this rate varied across counties (Figure 2-1). Some counties including Baltimore City, Kent and Allegany had overall average annual crude rates that were double (~12-15 per 100,000) the crude state rate, while other counties including Dorchester and Talbot had crude rates as low as 4 per 100,000 for the 10-year period assessed (Figure 2-1). Comparing average annual crude rates by county for the earlier 5-year study period (2003-2007) to the later 5-year study period (2008-2012), incidence remained fairly stable in some counties, including Baltimore City, Somerset and Charles counties (Table 2-2). In contrast, several counties including Allegany, Frederick and Garrett counties had lower average annual crude rates in the more recent 5-year study period. There were other counties including Kent, Washington and Prince

George's counties that experienced an increased average annual crude incidence rate in the later 5-year period (Table 2-2).

This geographic variation in rates was further confirmed in the space-time cluster detection analysis, which showed significant space-time clusters of higher and lower than expected rates of ICC incidence for certain counties in Maryland (Figure 2-2 & 2-3). After adjusting for county age distribution, the overall average annual adjusted statewide ICC incidence rate was 9.7 per 100,000. The most likely cluster, in the initial age adjusted cluster detection analysis, was a cluster of higher than expected (RR= 1.82; p-value<0.01) ICC incidence identified in Baltimore City (Table 2-3), which is a large metropolitan area [105] that has a high proportion of low income communities (annual median household income in Baltimore City for the time period 2003-2006 ranged from $29,162-$35,834 [96] compared to a statewide annual median household income range of $58,700- $65,250 [106] for the same time period). The cluster in Baltimore City was observed for the time period 2003-2006, and had an average annual adjusted incidence rate of 17.1 per 100,000 (Table 2-3). Another significant cluster identified, was a cluster of lower than expected (RR=0.78; p-value=0.01) ICC incidence rates that emerged in a group of fringe metropolitan [105] higher income counties in south-eastern Maryland (annual median household income across these counties for the time period 2005-2008, ranged from $63,005-$101,867 [96] compared to a statewide annual median household income range of $62,850 - $69,550 [106] for the same time period) (Table 2-3, Figure 2-2). This cluster of low rate had an average annual age and population size adjusted ICC incidence rate of 7.9 and was observed for the period 2005-2008.

After further adjustments for percent minority, percent screened for cervical cancer in the last 3-years, median household income, percent obese, and percent current smoker within each county, the overall average annual adjusted state ICC rate was 9.2 per 100,000. In this fully adjusted analysis, two significant clusters of low and 3 significant clusters of high rates emerged over the time period assessed (p-value ≤0.05) (Figure 2-3). Both clusters of low ICC rates occurred in the more recent calendar years of the study and were in primarily rural and suburban counties of various sizes. The most likely cluster in this analysis was a cluster comprising six counties in eastern Maryland with a dramatically lower incidence of ICC than expected (adjusted relative rate (aRR)=0.082, p-value<0.01) for the period 2009-2012. Median income for these mostly nonmetropolitan counties ranged from $39,630 - $88,406 and had a Pap screening prevalence range of 81.6%-95.2% [97]. The other cluster of low rate (aRR= 0.41; p-value<0.01) was a secondary cluster, which comprised two large fringe metropolitan counties west and northwest of Baltimore, for the period 2009-2012. In this time period, counties in this cluster, had a median income range of $60,543-$108,234 [96] and a screening prevalence range of 86.7%-92.2% [97]. Comparatively for this time period, 2009-2012, the statewide screening prevalence range was 82.1%- 86.7% [97] and median income ranged from $69,193 to $71,122 [106].

The first significant cluster of high ICC rate (aRR=2.52; p-value<0.001), identified in the fully adjusted analysis, was observed for the period 2005-2008 in Allegany and Garrett counties, which are respectively small metropolitan and rural counties in Western Maryland. For this cluster, median income ranged from $33,643 to $43,496 and Pap screening prevalence ranged from 72.5% to 83.6% within the time period identified. In

this time period, 2005-2008, prevalence of screening in Maryland ranged from 84.1% to 87.6% and median income ranged from $62,850 to $69,550.

Baltimore City remained a cluster of high rate (aRR=1.74, p-value<0.001) in the fully adjusted analysis, however unlike the initial cluster of high rate identified in the age and population size adjusted analysis, this cluster was for a more recent time period, 2009-2012. In Baltimore City, median income within this time period ranged from $38,186 to $39,077 and screening prevalence ranged from 82.0% to 84.9%. Another cluster of high rates (aRR=2.47, p-value=0.001) emerged in rural western Maryland in Frederick county for the period 2011-2012 (Table 2-3, Figure 2-3). For this time period, median income within this county ranged from $77,872 to $80,427 and Pap screening prevalence was 67.1%. The last cluster of high rate (aRR= 1.33) identified in the adjusted analysis was observed in the suburban large fringe metropolitan county of Montgomery; however, this cluster was not statistically significant (p-value= 0.24) and was for the period 2003-2006. Median income range for this cluster was $76,669-$87,019 and screening prevalence range was 85.3%-90.6%. Comparatively statewide screening prevalence range was 87.6%- 88.6% and median income ranged from $58,700 to $65,250 in this time period, 2003-2006.

DISCUSSION

In this retrospective space-time cluster detection analysis of ICC incidence in Maryland, most counties had consistently moderate ICC incidence across the time period examined. However, several hotspots of high and low incidence were also detected. These findings show that although overall statewide ICC incidence is generally low, there are areas, even

in the most recent time period that experienced an irregularly high incidence of ICC. Clusters of low ICC incidence identified provide evidence of the impact of state and county level efforts to address ICC in Maryland and suggest that ongoing prevention and control efforts have been highly successful in specific areas of the state. Understanding these remaining areas of anomalous ICC incidence can help to help prioritize additional interventions or outreach that may be most impactful.

The ICC clusters identified in Maryland by our study are not explained by the age distribution, average screening rates in the county, health status (smoking and obesity), median household income and health insurance coverage within counties contained in the clusters identified. Of course individual level impact of these factors remains, especially as most ICC cases are known to be underscreened or never screened [15,14,13]. Our adjustment for average county screening suggests the clusters observed are not due to availability of screening in the area, but to other barriers that affect screening in these women. In addition, we cannot rule out the potential for residual confounding even for the factors adjusted for in our analysis. Further, other factors that we did not have data on may contribute to the elevated rates in the clusters of high incidence including possible risk factors such as a lower proportion of women who seek follow-up testing after an abnormal Pap test result [107], delays in follow-up testing after an abnormal result [108,107] as well as a higher proportion of women living with HIV [109,110] within counties in the identified clusters of high incidence. Although highly effective treatments currently exist for cervical abnormalities, delays in follow-upon abnormal screening results, especially among minority groups have been associated with an increased cervical cancer incidence [108,107,111].

The average annual age adjusted incidence of 9.7 per 100,000 observed in our study for Maryland is comparable to the reported national rate of 7.7 per 100,000 within the same time period [31]. In addition, within our study period (2003-2012), the national average age annual adjusted ICC incidence decreased significantly at a rate of 1.3% [31]. In spite of the decrease in national rates and a comparable national and Maryland state average annual ICC rate, the findings of our cluster detection analysis support our study hypothesis. They indicate that even in recent time periods, the burden of ICC is uneven across smaller geographic units and that there are still some counties experiencing an anomalously high ICC incidence. Thus, identifying and investigating these units can further accelerate the decline of ICC incidence at the national and state levels.

Our analysis of variation in cervical cancer incidence among counties in Maryland has several strengths and to our knowledge this is one of the first studies to assess the space-time variation of ICC incidence at the county level. Our study included 10 years of data to allow for assessments of temporal variation, and incorporated information on county characteristics from different data sources to assess if there are significant space-time clusters that are not explained by the county characteristics. The detection of significant clusters of both high and low ICC incidence provides additional data that can be used to prioritize ICC needs at the county level and ensure effective ICC prevention and control.

This study also has some limitations. Our evaluation of a space-time variation in ICC incidence was conducted at the county level and could not explore potential heterogeneity in incidence rates that may be present at smaller geographic units, such as census tracts, within each county [112,51]. However, given the relatively low number of ICC cases, conducting our analysis at the county allowed for an adequate sample size within each

geographic unit [51]. A second limitation is that these county based findings and resulting inferences made about ICC risk at the county level may not hold true at smaller geographic units or for individuals within those counties[51,113].

In conclusion, the observed clusters of high and low ICC incidence provide evidence of a significantly non-uniform ICC incidence across counties in Maryland within the 10-year period assessed. The clusters of lower than expected rates identified provide evidence supporting the impact of state and local efforts to address ICC. While the clusters of higher than expected rates suggest that in spite of the progress made over time, some counties have seen an increased ICC incidence rate, which should be monitored and considered for targeted interventions.

Table 2-1. Characteristics at diagnosis of 2172 invasive cervical cancer cases 18 years or older, diagnosed in Maryland between 2003 to 2012

Descriptor	n (%)
Age at diagnosis, years	
≤29	99 (4.6)
30-39	402 (18.5)
40-49	576 (26.5)
50-59	439 (20.2)
60-69	314 (14.5)
≥70	342 (15.7)
Birth location	
United States	917 (42.2)
Maryland	411 (18.9)
DC, VA, PA	144 (6.6)
North East (other than PA) [a]	69 (3.2)
Midwest [b]	25 (1.2)
West coast [c]	7 (0.3)
South (other than DC, VA, MD) [d]	98 (4.5)
Other / U.S. region unknown	163 (7.5)
Outside United States	150 (6.9)
Africa	28 (1.3)
Europe	9 (0.4)
South America & Caribbean	65 (3.0)
Asia & Middle East	27 (1.2)
Other	21 (1.0)
Unknown	1105 (50.9)
Race	
Black	750 (34.5)
White	1254 (57.7)
Other	143 (6.6)
Unknown	35 (1.6)
Insurance status	
Uninsured	131 (6.0)
Private Insurance	748 (34.4)
Public Insurance	586 (27.0)
Other	345 (15.9)
Unknown	362 (16.7)

Descriptor	n (%)
Type of reporting source	
Medical provider/Health facility	1976 (91.0)
Lab only	155 (7.1)
Death certificate	41 (1.9)
Unknown	0 (0.0)
Grade	
I	213 (9.8)
II	537 (24.7)
III/ IV	627 (28.9)
Unknown	795 (36.6)
Metastasis	
No	1410 (64.9)
Yes	201 (9.3)
Unknown	561 (25.8)
Diagnostic confirmation	
Histology	1952 (89.9)
Cytology	76 (3.5)
Clinical	12 (0.6)
Unknown	132 (6.1)
Marital status	
Never married	591 (27.2)
Married/Domestic partner	817 (37.6)
Separated/Divorced	262 (12.1)
Widowed	216 (9.9)
Unknown	286 (13.2)

[a] Northeast: Connecticut Delaware Massachusetts Maine New Hampshire New Jersey New York Rhode Island Vermont [47]

[b] Midwest: Illinois Indianapolis Kansas Michigan Missouri Nebraska Ohio Wisconsin

[c] West coast: California Colorado Hawaii Washington [47]

[d] South: Alabama Arkansas Florida Georgia Kentucky Louisiana Mississippi North Carolina South Carolina Oklahoma Tennessee Texas West Virginia [47]

[e] Others: Guam

Table 2-2. Average annual crude incidence of invasive cervical cancer per 100,000, by counties in the state of Maryland, for the time periods 2003-2007 and 2008-2012

County	Average annual crude rate per 100, 000 [a]	
	2003-2007	2008-2012
Charles	6.1	4.6
Somerset	6.3	2.5
Frederick	6.9	8.6
Caroline	7.1	7.1
Garrett	8.0	9.3
Harford	8.0	7.6
Anne Arundel	8.3	8.8
Cecil	8.4	6.2
Carroll	8.6	8.6
Montgomery	8.7	10.3
Talbot	8.8	11.4
Prince George's	8.9	6.7
Calvert	9.7	4.8
Queen Anne's	10.1	8.5
Baltimore City	10.2	9.2
Baltimore County	10.4	7.4
Washington	10.6	9.0
Kent	10.6	7.3
Wicomico	11.2	9.4
Dorchester	11.3	7.8
Howard	12.0	12.0
Worcester	15.0	14.0
St. Mary's	15.4	15.4
Allegany	15.7	10.7

[a] Rates are listed in an ascending order of average annual crude incidence rate, observed for the period 2003-2007.

Table 2-3. Space-time clusters of invasive cervical cancer incidence rates by county in the state of Maryland, 2003-2012.

Space-Time Clusters	Average annual adjusted rates per 100,00	Standardized Incidence Ratio	Relative Risk	p-value	Time period, years
Age-Adjusted [a]					
Most likely cluster: Baltimore City	17.1	1.76	1.82	<0.001	2003-2006
Secondary Clusters:					
• Montgomery, Prince George's, Howard, Charles, Anne Arundel	7.9	0.82	0.78	0.014	2005-2008
• Caroline, Talbot and Queen Anne's	1.0	0.11	0.11	0.228	2011-2012
Fully Adjusted [b]					
Most likely cluster: Dorchester, Talbot, Caroline, Wicomico, Calvert and Queen Anne's	0.8	0.084	0.08	<0.001	2009-2012
Secondary Clusters:					
• Baltimore City	15.5	1.68	1.74	<0.001	2009-2012
• Carroll and Howard	3.8	0.42	0.41	<0.001	2009-2012
• Frederick	22.4	2.44	2.47	0.001	2011-2012
• Allegany and Garrett	22.9	2.50	2.52	0.002	2005-2008
• Montgomery	11.9	1.30	1.33	0.150	2003-2006

[a] Average annual statewide ICC incidence for the age-adjusted analysis was 9.7 per 100,000 and the analysis was adjusted for county age distribution.

[b] Average annual statewide ICC incidence for the adjusted analysis was 9.2 per 100,000 and the analysis adjusted for age distribution, percent minority, percent screened for cervical cancer in the last 3-years, median household income, prevalence of obesity and smoking within each county.

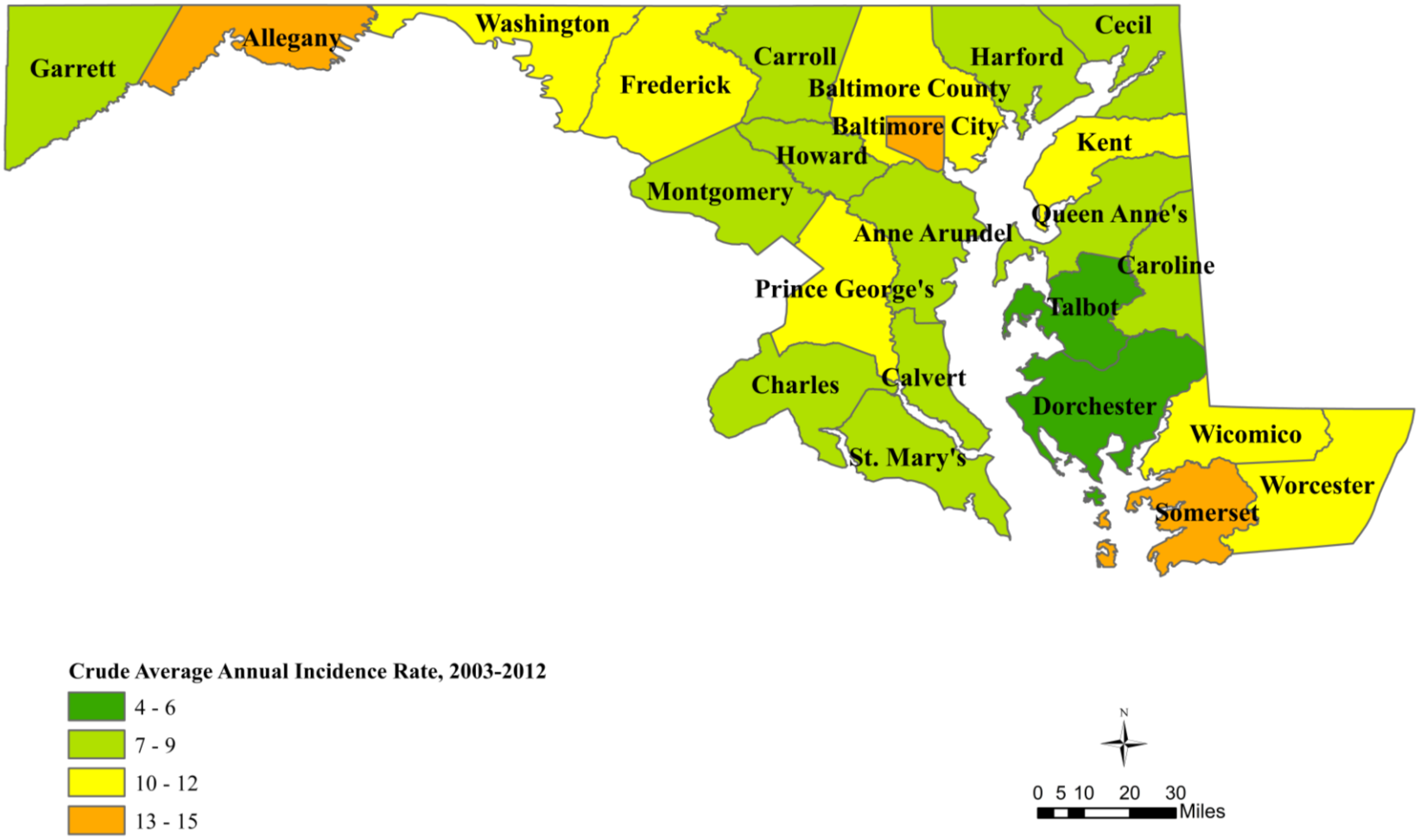

Figure 2-1. Choropleth map of average annual crude incidence of invasive cervical cancer per 100,000 women by county in Maryland, 2003-2012

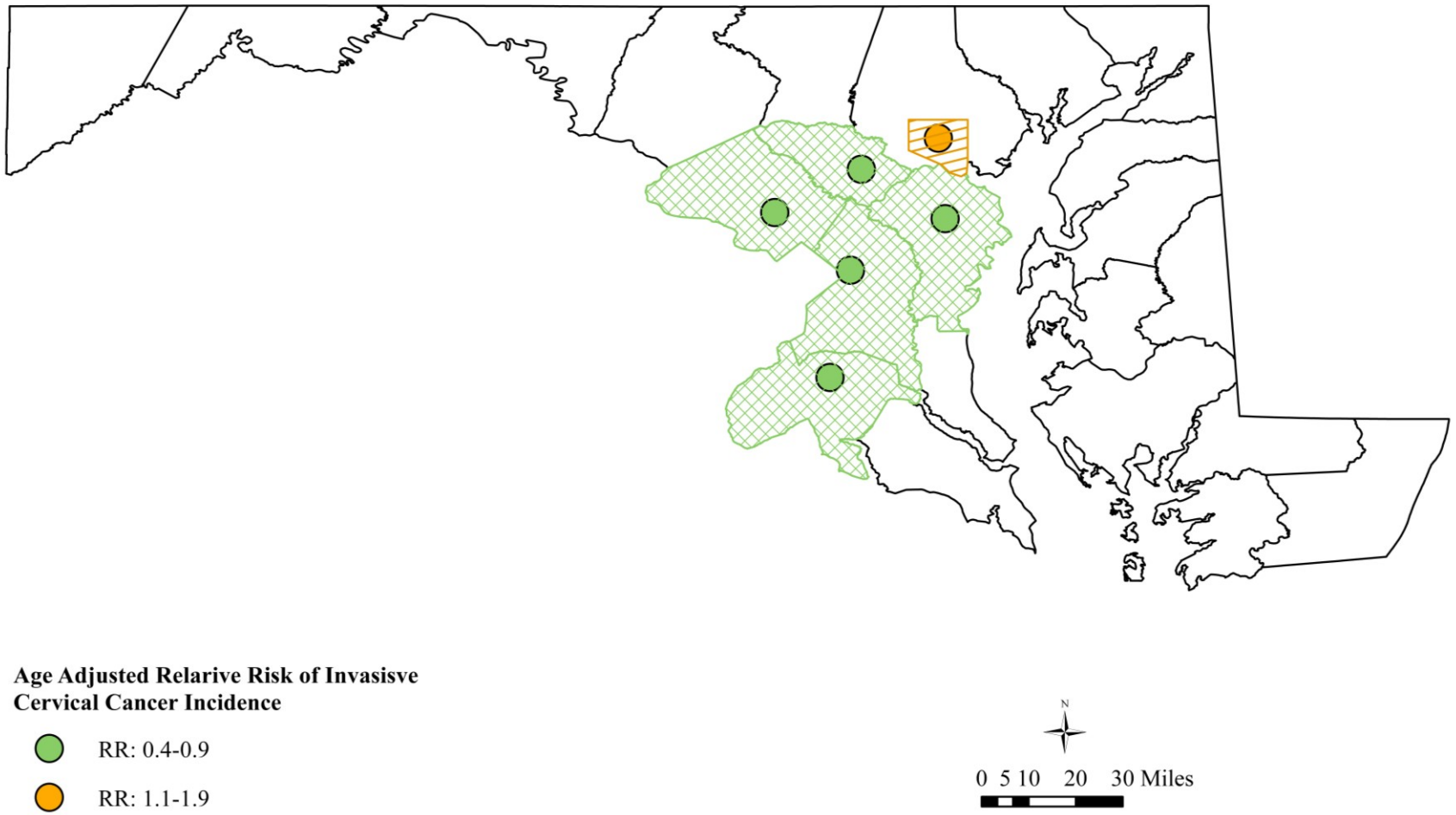

Figure 2-2. Age-adjusted map of significant ($p \leq 0.05$) space-time clusters of high (red) and low (green) invasive cervical cancer incidence rates by county in Maryland, 2003-2012.

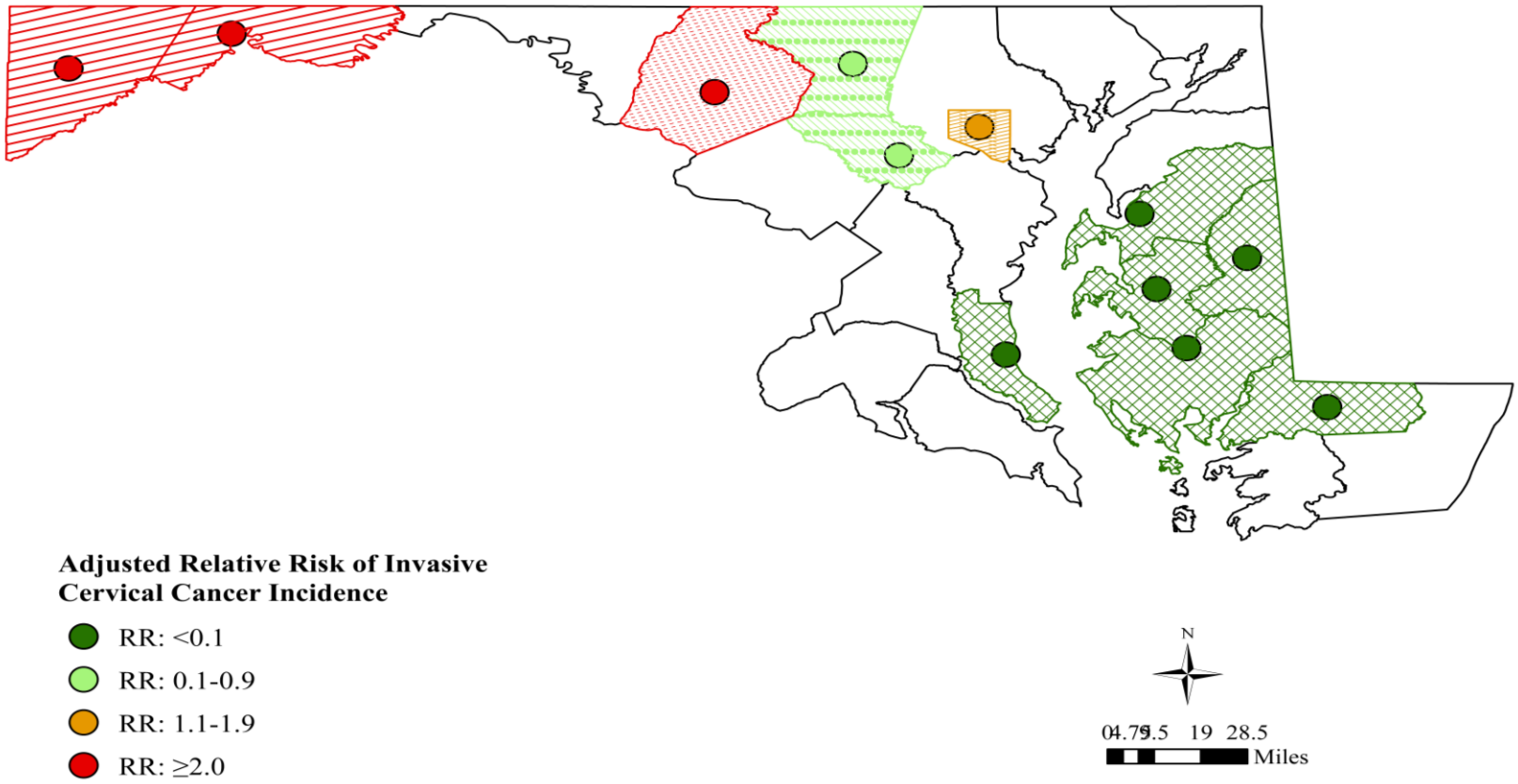

Figure 2-3. Adjusted map of significant (p≤0.05) space-time clusters of high and low invasive cervical cancer incidence rates by county in Maryland, 2003-2012. Adjusted for age distribution, median household income, cervical cancer screening rates, prevalence of smoking and obesity within each county.

CHAPTER 3: SCREENING

Pap Test Utilization Among Women Living With HIV Enrolled In Primary Care: A 10-Year Longitudinal Study

ABSTRACT

Objective:

Previous evaluations of Pap testing among women living with HIV (WLWH) have mostly been cross-sectional or had relatively short follow-up Therefore this study was conducted to longitudinally describe utilization and determinants of Pap testing among WLWH over a 10-year period.

Methods:

Data were obtained by linking medical and pathology records of WLWH seen at Johns Hopkins Hospital between 2005 and 2014. Determinants were assessed using Prentice, Williams, Peterson models.

Results:

Of 554 WLWH in care for ≥18 months, a large proportion (79%) received Pap testing, however only 11% consistently received Pap testing at the recommended annual interval. Some women (5%) were consistently under-screened (tested at intervals longer than 18-months) and 21% did not receive any Pap testing at during follow-up.

WLWH with decreased likelihood of screening included older women (per decade aHR=0.94, 95%CI: 0.89, 0.99), injection drug users (aHR=0.80, 95%CI: 0.70, 0.93), white women (aHR=0.85, 95%CI: 0.72, 1.00) and those who had lived for a longer time with HIV (per decade aHR=0.90, 95%CI: 0.81, 0.99). In contrast, only women with a prior abnormal Pap result were more likely to receive Pap testing (aHR= 1.66, 95%CI: 1.44, 1.92). CD4 cell count and health insurance were not significant determinants.

Conclusion:

Although many WLWH in care receive Pap testing, some WLWH remain unscreened or underscreened. Significant determinants of Pap testing for WLWH include socio-demographic factors and a prior abnormal result. These present potential targets in an urban HIV care setting for closer monitoring and directed interventions to improve utilization among WLWH.

INTRODUCTION

In 2012, the Centers for Disease Control estimated about 284, 500 women were living with HIV (WLWH) in the United States [114]. Even with tremendous improvements in clinical management of HIV, WLWH still represent an important high-risk subgroup for cervical cancer with their current incidence of cervical cancer being 4-fold higher than that of the general population [24]. Additionally, treatment response and survival rates are much lower among WLWH diagnosed with cervical cancer than for women in the general population [115,116]. Thus, routine Pap testing is recommended and is important for all WLWH.

Until recently, screening guidelines for WLWH were similar to those for the general population, suggesting annual Pap testing, except for women newly diagnosed with HIV who were recommended to receive a Pap test twice in the first year post HIV diagnosis [117]. More recently, guidelines in the general population have changed to suggest Pap testing every three years after a normal Pap [118]. Guidelines for WLWH also changed in 2015 to suggest a three-year follow-up interval among women with 3 consecutive normal Pap test results [66]. However, by virtue of their higher risk, annual Pap testing is still recommended for WLWH with one or two consecutive normal Pap tests results [66].

in its 2012 report to congress the United States Preventive Services Task Force identified the limited evidence base on utilization of cervical cancer screening as one of the barriers to effective prevention and control in the US [119]. Indeed, among women diagnosed with cervical cancer in the US, most were enrolled and regularly accessing healthcare services but were never screened (50%) or underscreened (10%) in the years prior to diagnosis [12,14]. Furthermore, despite the recommendation for frequent Pap testing

among WLWH, some previous studies suggest that Pap testing remains underutilized, even for WLWH enrolled in clinical care [16,61,21,22]. Initial studies exploring barriers to Pap testing among WLWH identified older age, blacks and other racial minorities, low socioeconomic status, low CD4 cell count and low level of education to be associated with the underutilization of Pap test services by WLWH [120,61,16,22].

In one of the largest studies to date of Pap test utilization among WLWH, a cross-sectional survey of WLWH across 18 states reported a sizable proportion (23%) did not receive Pap testing [61] . Focused group interviews on utilization of gynecologic services by WLWH at the Moore clinic of Johns Hopkins in 2008 suggested 22% of women never received a Pap test in the preceding year [21]. Relying solely on electronic records, a study of WLWH in care at Boston Medical Center reported an even higher proportion (47%) of women did not receive annual Pap testing [16]. However, these previous studies were largely been cross-sectional in nature, relied on self-reports, or followed WLWH for a relatively short period of time [16,17,21-23]. Thus, to address these limitations, the current study evaluated utilization and determinants of cervical Pap testing among WLWH enrolled in care at Johns Hopkins Hospital over the previous 10-years.

METHODS

Study Design and Population

A longitudinal study of WLWH enrolled in clinical care within a retrospective 10-year period, from January 1, 2005 to December 31, 2014, was performed. This study utilized data collected as part of the Moore Clinic cohort, which is composed of people living

with HIV in Baltimore who are followed up longitudinally through medical record based abstraction of demographic, behavioral and clinical data at regular six months intervals [121]. Among 669 women in the cohort and in care during this timeframe, the analysis was restricted to 554 WLWH who were: at least 18 years old, had basic demographic information available in their medical records and had clinical follow-up for at least 18 months (to allow an opportunity to be screened). For 54 women, who met the inclusion criteria and were newly diagnosed with HIV, only data collected on or after HIV diagnosis were utilized in this analysis; data prior to diagnosis was excluded.

Outcome

The primary outcome of interest for this study, receipt of a Pap test, was defined using a binary indicator (yes or no). As this was a recurring outcome, women could experience multiple Pap tests during clinical follow-up. After every Pap test, each woman was considered to be at risk for her next event (Pap test) until the end of time spent in clinical care or until the end of the 10-year period.

Although all WLWH are recommended to have at least an annual Pap test, we allowed a window of 18 months before considering a participant as not having received an annual Pap. This expanded period allowed us to be specific in our definition of underscreening, Further, to ensure accuracy of data used in this study, individual medical records were linked to the Johns Hopkins Hospital pathology database using unique patient identifiers.

Determinants of Pap Testing

Information assessed at entry and treated as fixed variables in the analysis included: smoking status (current or never/former), injection drug use (yes or no), race (black, white or other), date of HIV diagnosis, and body mass index (BMI) calculated using

recorded weight and height (underweight / normal: ≤24.9, overweight: 25-29.9 or obese≥30.0). Time-varying variables evaluated at entry and at each screening visit, included: type of health insurance (public {Medicare/Medicaid}, private, Ryan White health insurance and uninsured/out of pocket payment) and current CD4 cell count. At screening visits where information on time varying variables was not available, information about those variables from a preceding visit was utilized. Results of the preceding Pap test were also assessed at each screening visit and categorized as: normal ("negative for intraepithelial lesion or malignancy"), atypical squamous cells of undetermined significance (ASC-US) or atypical glandular cells of undetermined significance (AGUS), low-grade squamous intraepithelial lesions (LSIL), and high-grade squamous intraepithelial lesions (HSIL) or atypical squamous cells- cannot exclude HSIL (ASC-H) [122].

Statistical Analysis

Participants were described at entry using median values with corresponding interquartile range (IQR) estimates for continuous variables and percentages for categorical variables. The total number of Pap tests received during follow-up and the median time interval between each Pap test were also assessed. A Kruskal–Wallis test was used to compare median Pap test intervals by order of Pap test received and by results of the preceding Pap test. Linear trends were assessed using a nonparametric test for trend.

Prentice, Williams, Peterson gap time models (PWP-GT) were used to evaluate the determinants of Pap testing and follow-up for each woman was divided into multiple sets of time between Pap tests. These PWP-GT models are multiple failure time to event models that use a conditional risk set approach of time since each prior event to account

for the multiple time periods within the same women at risk for the event [123]. PWP-GT are variance corrected models, which adjust the covariance matrix of estimators to account for the dependent nature of the outcome [123].

The unadjusted hazard ratio (HR) and 95% confidence interval (95% CI) for each factor were assessed. For continuous variables, effects were explored as both continuous and categorical variables and rescaling in multiples of ten was done on the continuous scale to allow for easy interpretation. Factors observed to be significant in unadjusted analysis or those identified by previous studies were included in the adjusted analysis. The adjusted model from which adjusted hazard ratios (aHR) were obtained included age, race, injection drug use, number of years since HIV diagnosis, results of preceding Pap test, CD4 cell count and type of health insurance as covariates. Goodness of fit for the adjusted model was assessed using Cox-Snell residuals.

All statistical tests were two sided and with an alpha ≤ 0.05. Data management and analysis were carried out in STATA 14 [102]. The institutional review board of Johns Hopkins Medical Institutions approved this study.

RESULTS

Study population

There were 554 WLWH who contributed 3,177 person-years to the study and were followed for a median of 5.7 years (IQR: 3.7-7.9). Forty-two percent of participants were in care and entered our analysis in the first year of the 10-year study period, 2005-06, with another 25% and 21% of participants entering the study in 2007-8 and 2009-10,

respectively (Table 3-1). At entry, participants had a median age of 41 years (IQR: 34-48), were predominantly black (79%), and many reported a current smoking status (57%) (Table 3-1). Median CD4 count at entry was 307 cells/ μl (IQR: 127-510), and median HIV viral load at entry was 7712 copies/ml (IQR: 400-53693).

Utilization of Pap testing

Although a large proportion of women received Pap testing (79%), a sizeable proportion (21%) never received Pap testing during study follow-up (Figure 1a). Among those who received at least one Pap test, some received only one or two (31%), while others had three (12%), four (10%) and five or more (26%) Pap tests during follow-up (Figure 3-1a).

As expected, women who were in care longer were more likely to receive Pap testing than women with shorter time in care (Figure 3-1b). Median time in care for women who received at least one Pap test during follow-up was 5.1 years (IQR: 3-6.9) compared to 3.8 years (IQR: 2.3-5.7) among women who never received a Pap test during clinical follow-up at Johns Hopkins Hospital. The total number of Pap tests received increased linearly with a longer median time in care (Figure 3-1b; np trend <0.001).

The overall median interval between successive Pap tests during follow-up was 11.3 months (IQR: 6.2-17.2). However, median time from entry to the first Pap was longer (17.9 months; IQR: 12.0-32.6, Figure 3-2) than the recommended annual interval, and women who had only one Pap had a longer median time from entry to Pap than women who had 2 or more Pap tests (19.6 vs 7.6 months). After the first Pap, median interval remained fairly consistent between subsequent Pap tests and with guideline recommendations (Figure 3-2).

Using a more stringent definition of screening of twelve months, only 11% of women consistently received Pap test according to guideline recommendations. This was 19% of women who received two or more Paps during follow-up, highlighting the potential for underscreening. Also of note, 5% of women screened consistently received Pap test at intervals longer than 18 months.

Results of 60% of the 1,410 Pap tests conducted during follow-up were reported as normal. Abnormal Pap results included ASC-US/AGUS (13% of all Paps), LSIL (13%), and HSIL/ASC-H (7%). Nine (<1%) of the Pap tests received did not have documented results.

Median interval between consecutive Pap tests varied significantly ($p<0.001$) by results of the preceding Pap test. For women with a normal result in the preceding Pap test, median interval to the subsequent Pap was 14.3 months (IQR: 10.7-20.5) (Figure 3-3). However, for women with an abnormal Pap result, this interval was shorter. Specifically, median interval for women with a preceding Pap test result of ASC-US/AGUS, LSIL or HSIL/ASC-H was 12.0 (IQR: 8.0-20.1), 11.1 (IQR: 7.2-16.5) and 11.0 (IQR: 8.7-16.5) months respectively. For women with an unknown Pap test result this interval was 13.8 months (IQR: 10.8-18.2).

Determinants of Pap testing

Several determinants of Pap test utilization were identified (Table 3-2). In unadjusted analysis older age (per decade, HR=0.90, 95%CI: 0.85, 0.95), white women (HR=0.84, 95%CI: 0.72, 0.99), injection drug users (HR= 0.79, 95%CI: 0.68, 0.91), women diagnosed with HIV for a longer time (per decade, HR=0.93, 95%CI: 0.79, 0.96) and those with an elevated CD4 cell count (per 100 cells/ μL, HR=0.98, 95%CI: 0.96, 1.00)

were all significantly less likely to receive a Pap test, each $p < 0.05$. In contrast, women with Ryan White health insurance coverage compared to women with Medicaid/Medicare (HR=1.27, 95%CI: 1.06, 1.52) and those with a previous abnormal Pap test result (compared to a normal result) of either ASC-US/AGUS (HR= 1.47, 95%CI: 1.22, 1.76), LSIL (HR=1.75, 95%CI: 1.45, 2.10) or HSIL/ASC-H (HR=2.22, 95%CI: 1.55, 3.17) were more likely to receive a Pap test. Former smokers and those who had never smoked were also more likely to receive a Pap test than current smokers (HR=1.14, 95%CI: 1.00, 1.30).

In the adjusted analysis, women of older age (aHR=0.93, 95%CI: 0.89, 0.98), white women (aHR=0.85, 95%CI: 0.72, 1.00), injection drug users (aHR=0.80, 95%CI: 0.70, 0.93) and women who had lived with HIV for a longer time (aHR=0.90, 95%CI: 0.81, 0.99) remained significantly less likely to receive a Pap test. By contrast, women with a previous abnormal Pap test result of ASC-US/AGUS (aHR=1.40, 95%CI: 1.14, 1.72), LSIL (aHR=1.76, 95%CI: 1.45, 2.13) or HSIL/ASC-H (aHR=1.93, 95%CI: 1.40, 2.66) remained significantly more likely to receive a Pap test. After adjusting for other variables, CD4 cell count and insurance were not significantly associated with Pap testing (Table 3-2).

DISCUSSION

In our longitudinal assessment of Pap testing among WLWH enrolled in clinical care, we observed that 21% of WLWH did not receive any Pap testing during follow-up. Additionally, only 11% of women consistently received a Pap test at the recommended annual interval and 5% were consistently underscreened. The likelihood of receiving a

Pap test for WLWH enrolled in clinical care, was associated with some of the socio-demographic, clinical and behavioral factors examined. Older women, white women, intravenous drug users and women who had lived with HIV for a longer time were less likely to receive a Pap test. These findings contribute to the existing evidence base on Pap test utilization among WLWH enrolled in clinical care. They suggest groups that may need to be closely monitored to ensure receipt of Pap testing as recommended.

The associations observed between older age, injection drug use and a decreased likelihood of receiving a Pap test are consistent with the findings of previous studies that also reported that these biologic and behavioral risk factors can affect screening frequency [16,124,21]. Even though Pap testing is recommended throughout a WLWH's life [66] older women are often perceived to have a lower risk of cervical cancer, which makes them less likely to receive Pap testing. Compared to non-users, injection drug users living with HIV have been noted to only partially engage in care [125] and as such may not have the opportunity to receive all required medical services. This might explain the decreased association observed for injection drug users. Although several previous studies have reported white WLWH are more likely to receive Pap testing compared to black WLWH, we observed a marginally lower likelihood of screening among white WLWH. This finding is consistent with a previous study conducted in an urban health facility, which reported a twofold increased odds of non-adherence among white WLWH compared to black WLWH [16]. This may in part reflect differential healthcare access and demographic profile of urban black WLWH compared to black WLWH in other settings [126,127].

Our finding of a decreased likelihood of Pap testing among women with a longer time since HIV diagnosis, independent of older age, has not been previously reported. This decrease is potentially a result of the greater number of competing health priorities that develop as people live longer with HIV, which decreases their likelihood of receiving Pap testing. Similar to what we found, some studies have identified a prior abnormal Pap result as a predictor of future screening in both the general population [128] and WLWH [16,129]. In this study, we could not discern whether the increased screening was driven by provider or patient motivations for screening.

The proportion of unscreened women in our study is higher than that reported for the general US population [130] and falls well above the healthy people 2020 target of 7% [131]. However, the proportion of unscreened women observed in our study is consistent with previous studies. These previous studies have reported 19-25% of WLWH in the United States do not receive Pap testing [23,61,16,22]. In addition, our findings suggest that even when women are in care over several years in the same clinic some WLWH remain underscreened or unscreened. This study could not however, evaluate whether women were refusing screening when offered.

Pap test intervals for WLWH have not been widely assessed and reported. To our knowledge this is one of the few evaluations of time intervals between Pap test for WLWH. Although the overall median interval between Pap test was fairly consistent with prevailing guideline recommendation [132], the proportion of women consistently screened throughout clinical follow-up, at or around the recommended annual interval, was low. Some women were consistently underscreened and intervals varied widely for the first few Paps. This suggests that although a sizeable proportion of WLWH receive

Pap testing regularly while in care, there are other WLWH who are infrequently screened and have much longer Pap tests intervals than guideline recommendations.

This study has several strengths including our use of a comprehensive longitudinal history of Pap testing, confirmed by pathology data. Unlike previous studies, the longer period evaluated in this study allowed description of screening patterns and time between Pap tests to be assessed. Our study may not have captured Pap test received outside of Johns Hopkins Hospital, so we cannot exclude the possibility that some women were screened elsewhere and therefore the prevalence of underscreening would be overestimated in this study. To minimize the potential for this to occur, our analysis was restricted to participants who were enrolled in primary care for at least 18 months. In addition, most (~85%) of the cohort participants in this study are known to access *all* of their healthcare needs through the Johns Hopkins network [121]. We could not evaluate variables not routinely captured in medical records on factors such as patient understanding of the importance of Pap testing or personal or access barriers to screening.

Our findings provide additional evidence that although most WLWH receive Pap testing, some women in clinical care are not screened and some women receive Pap testing at intervals longer than recommended. Characteristics of WLWH least likely to receive Pap testing include older women, women with a longer time since HIV diagnosis, injection drug users and white women, which present potential targets in an urban HIV care setting for closer monitoring and directed interventions to improve Pap screening in WLWH.

Table 3-1. Characteristics of 554 WLWH at their first clinic visit within the study period (2005-2014)

Characteristic	n (%)
Age (years): Median (IQR)	41 (34-48)
<30	79 (14.3%)
30-39	162 (29.2%)
40-49	201 (36.3%)
≥50	112 (20.2%)
Race	
Black	440 (79.4%)
White	92 (16.6%)
Other	22 (4.0%)
Baseline CD4 cell count (cells/μL): Median (IQR)	307 (127-510)
<200	180 (32.5%)
200-499	229 (41.3%)
≥500	144 (26.0%)
Unknown	1 (0.2%)
Baseline HIV viral load (copies/mL): Median (IQR)	7712 (400-53693)
Unknown	5 (0.9%)
Time since HIV diagnosis (years): Median (IQR)	2.1 (0.1-8.9)
0-4	326 (58.8%)
5-14	158 (28.5%)
≥15	63 (11.4%)
Unknown	7 (1.3%)
BMI (kg/m^3): Median (IQR)	27.43 (23.6-33.1)
Underweight: <18.5	15 (2.7%)
Normal: 18.5-24.9	119 (21.6%)
Overweight: 25-29.9	118 (21.5%)
Obese: ≥30.0	149 (27.1%)
Unknown	149 (27.1%)
Smoking status	
Current	315 (56.9%)
Former	33 (6.0%)
Never/ Unknown	206 (37.2%)

Characteristic	n (%)
Injection drug use	
Yes	146 (26.4%)
No	408 (73.7%)
Calendar years of study entry	
2005-2006	234 (42.2%)
2007-2008	142 (25.6%)
2009-2010	118 (21.3%)
2011-2015	60 (10.8%)
Type of health insurance	
Public (Medicaid/Medicare)	89 (16.1%)
Private	42 (7.6%)
Ryan White	49 (8.8%)
Uninsured/Out of pocket	6 (1.1%)
Unknown	368 (66.4%)
Total amount of follow-up in clinical care (years**)**: Median (IQR)	5.7 (3.7-7.9)

Table 3-2. Factors associated with utilization of Pap Testing by WLWH enrolled in care at the Moore Clinic of Johns Hopkins Hospital, 2005-2014

Variable	Hazard Ratio	95% Confidence Interval	p-value	Adjusted Hazard Ratio	95% Confidence Interval	p-value
Age, per 10 years	**0.90**	**(0.85 - 0.95)**	**<0.01**	**0.93**	**(0.89 - 0.98)**	**0.01**
<30 (ref)	1.00	--	--	1.00	--	--
30-39	0.97	(0.80 - 1.16)	0.72	1.01	(0.84 - 1.21)	0.94
40-49	0.93	(0.78 - 1.11)	0.43	0.98	(0.82 - 1.16)	0.79
≥50	**0.72**	**(0.59 - 0.88)**	**<0.01**	**0.81**	**(0.67 - 0.99)**	**0.04**
p for trend	**<0.01**			**0.02**		
Race						
Black (ref)	1.00	--	--	1.00	--	--
White	**0.84**	**(0.72 - 0.99)**	**0.03**	**0.85**	**(0.72 - 1.00)**	**0.04**
Other	0.87	(0.60 - 1.24)	0.44	0.77	(0.53 - 1.11)	0.16
Injection drug use	**0.79**	**(0.68 - 0.91)**	**<0.01**	**0.80**	**(0.70 - 0.93)**	**<0.01**
Time since HIV diagnosis, per 10 years	**0.93**	**(0.89 - 0.98)**	**<0.01**	**0.90**	**(0.81 - 0.99)**	**0.03**
0-4 (ref)	1.0	--	--	1.00	--	--
5-14	**0.78**	**(0.69 - 0.89)**	**<0.01**	**0.84**	**(0.74 - 0.95)**	**0.01**
≥15	**0.84**	**(0.72 - 0.99)**	**0.04**	0.88	(0.74 - 1.05)	0.17
p for trend	0.15			**0.08**		
Results of preceding Pap test						
Normal (ref)	1.0	--	--	1.00	--	--
Any abnormal	**1.66**	**(1.45 -1.90)**	**<0.01**	**1.66**	**(1.44 - 1.92)**	**<0.01**
ASC-US or AGUS	**1.47**	**(1.22 - 1.76)**	**<0.01**	**1.40**	**(1.14 - 1.72)**	**<0.01**
LSIL	**1.75**	**(1.45 - 2.10)**	**<0.01**	**1.76**	**(1.45 - 2.13)**	**<0.01**
HSIL or ASC-H	**2.22**	**(1.55 - 3.17)**	**<0.01**	**1.93**	**(1.40 - 2.66)**	**<0.01**
Never received Pap test / Unknown	1.18	(0.91 - 1.53)	0.22	1.21	(0.93 - 1.55)	0.15

Variable	Hazard Ratio	95% Confidence Interval	p-value	Adjusted Hazard Ratio	95% Confidence Interval	p-value
CD4 cell count, cells/100μL	**0.98**	**(0.96 - 1.00)**	**0.04**	0.99	(0.97 - 1.01)	0.29
≥500 (ref)	1.0	--	--	1.00	--	--
200-499	1.09	(0.94 - 1.27)	0.25	0.97	(0.85 - 1.09)	0.59
<200	1.09	(0.94 - 1.26)	0.26	1.00	(0.86 - 1.16)	0.98
p for trend	0.27			0.90		
Type of health insurance						
Public (ref)	1.0	--	--	--	--	--
Private	1.11	(0.94 - 1.32)	0.23	1.04	(0.87 - 1.25)	0.67
Ryan White	**1.27**	**(1.06 - 1.52)**	**0.01**	1.16	(0.96 - 1.40)	0.13
Uninsured/Out of Pocket	1.32	(0.85 - 2.06)	0.22	1.20	(0.77 - 1.87)	0.43
Unknown	0.94	(0.82 - 1.07)	0.34	0.87	(0.76 - 0.99)	0.04
BMI, kg/per 100 m^3	1.03	(0 .96 -1.11)	0.38	--	--	--
Underweight / Normal: ≤24.9 (ref)	1.0	--	--	--	--	--
Overweight: 25-29.9	1.03	(0.87 - 1.23)	0.70	--	--	--
Obese: ≥30.0	1.09	(0.93 - 1.28)	0.30	--	--	--
Unknown	0.98	(0.84 - 1.16)	0.85	--	--	--
p for trend	0.76					
Smoking status						
Current (ref)	1.0	--	--	--	--	--
Never / Former	**1.14**	**(1.00 -1.30)**	**0.052**	--	--	--
Unknown	**1.31**	**(1.11 - 1.55)**	**<0.01**	--	--	--

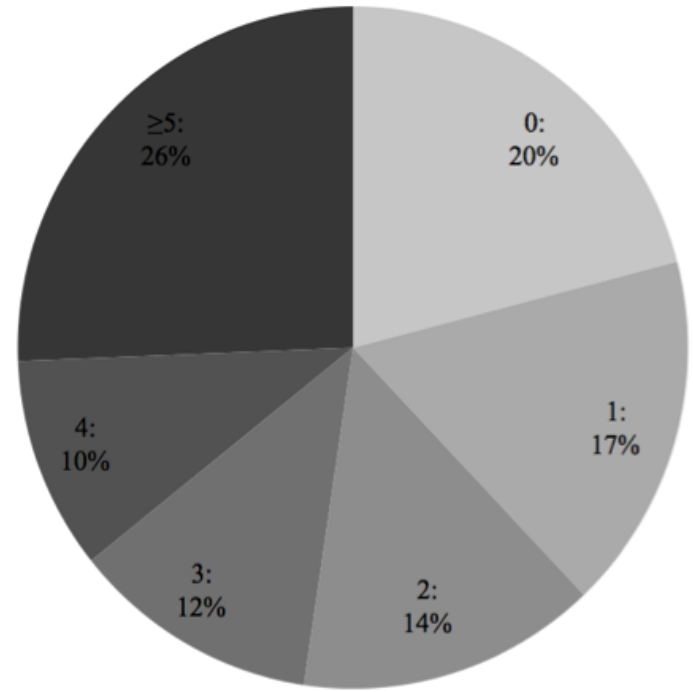

Figure 1a

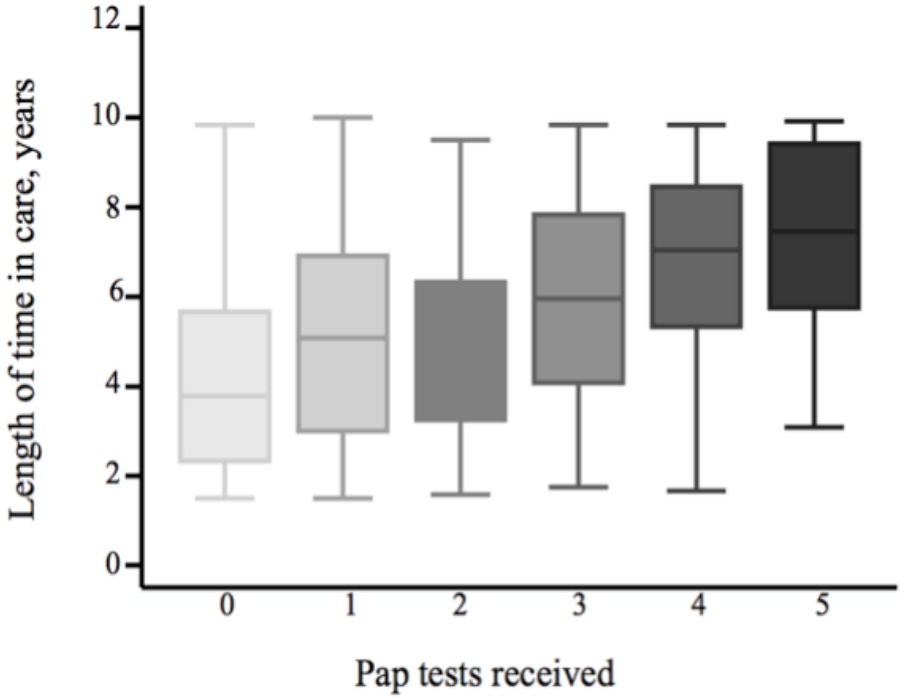

Figure 1b

Figure 3-1a. Percent of women receiving 0, 1, 2, 3, 4, and 5 or more Pap tests during their follow-up **3-1b.** Total time in care (number of years) within study period, by total number of Pap tests received by each participant

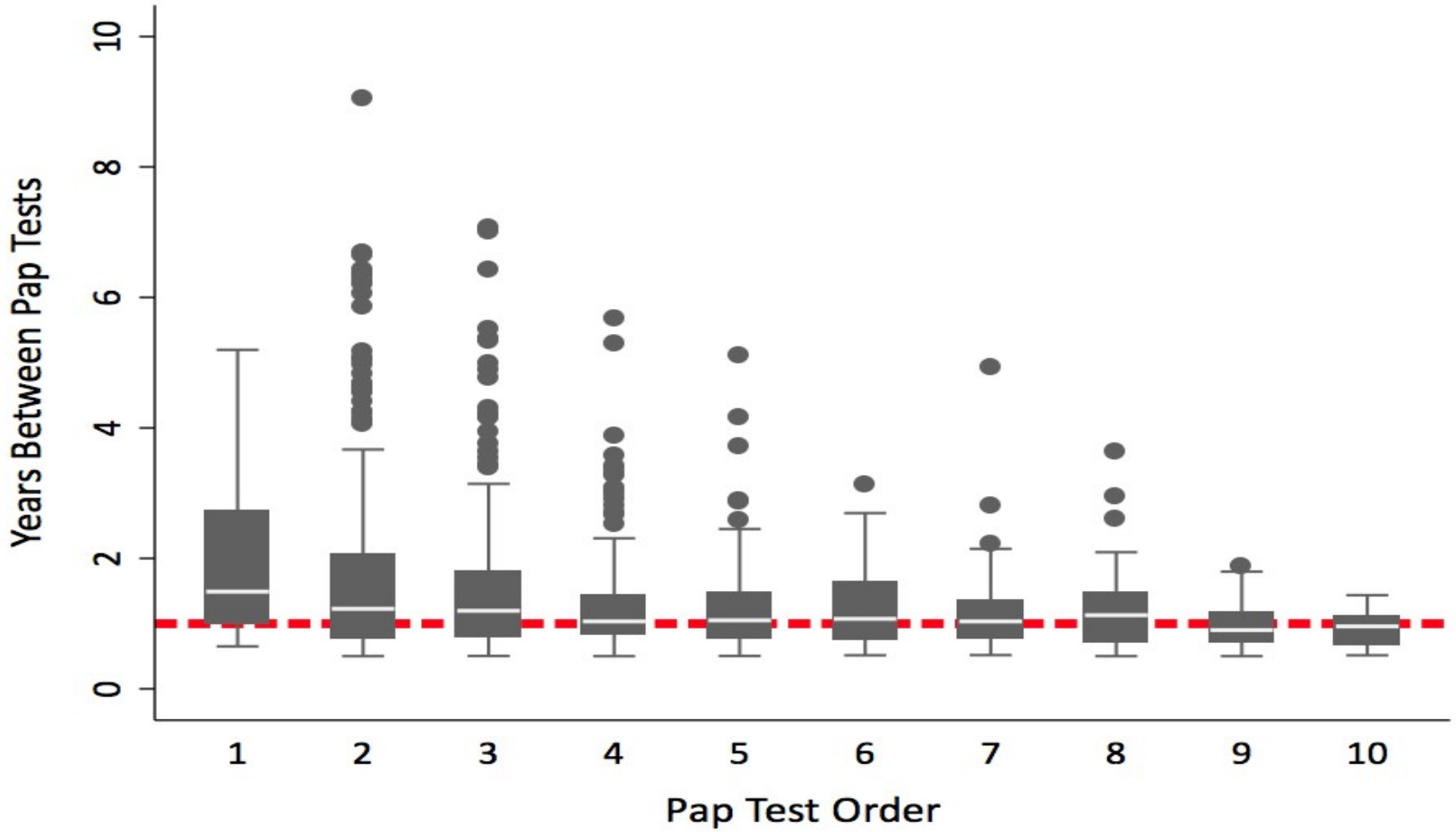

Figure 3-2. Among women screened, time interval (number of years) between current Pap and previous Pap test, by Pap test order. In this graph, category 1 represents the 1st Pap within the study, which is time from entry until first Pap. Category 2 represents the time to

the 2nd Pap (from the first Pap), among women who had at least 2 Paps, etc. Median and interquartile range is shown. Dotted line represents recommended screening interval of 12 months.

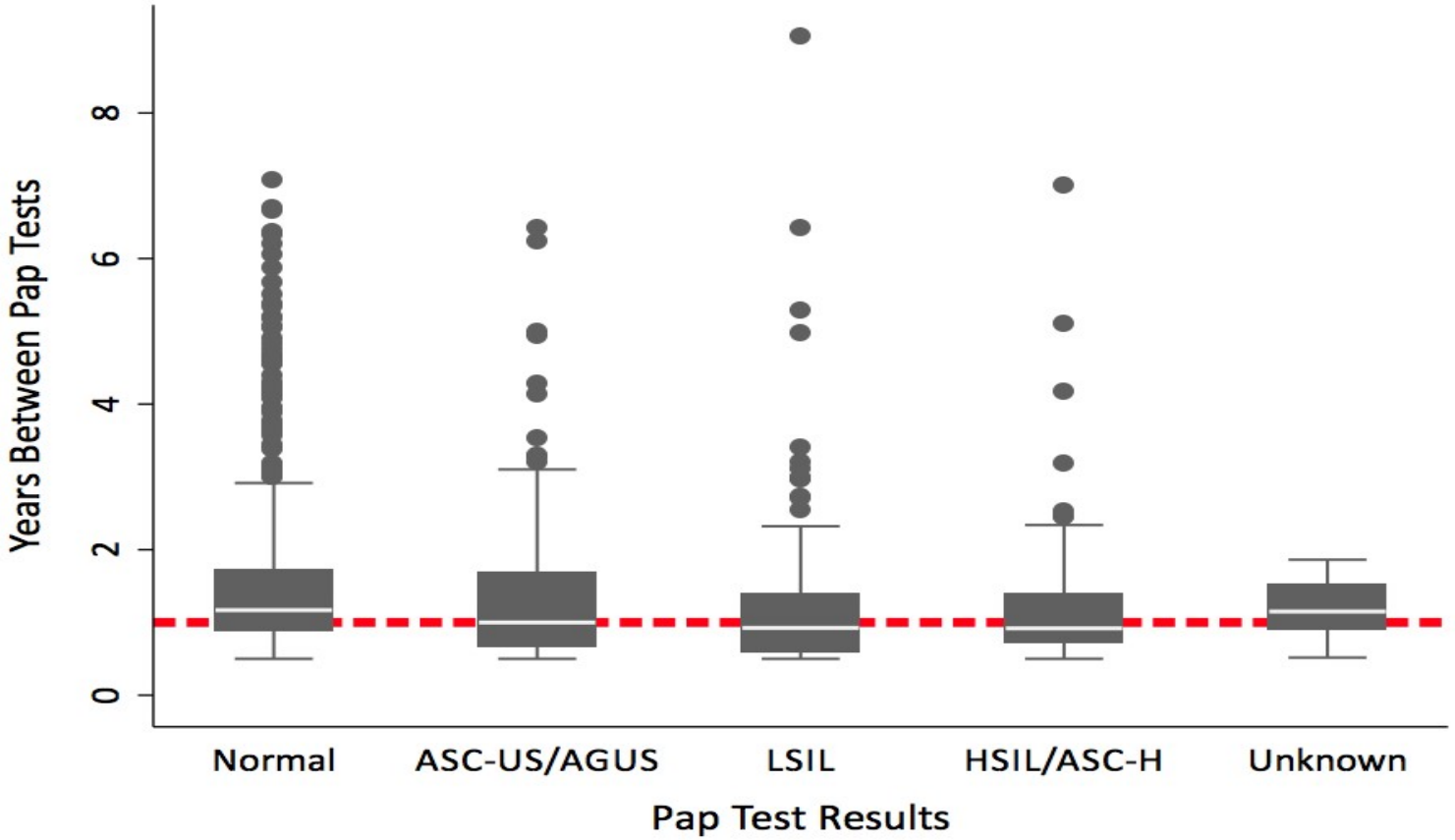

Figure 3-3. Among women screened, time interval (number of years) between previous and current Pap test, by the preceding Pap test results. . In this graph, category 1 represents the time interval from a normal Pap test result until the next Pap test.

Category 2 represents the time to the next Pap test, among women with an abnormal Pap test result of ASC-US/AGUS, etc. Median and interquartile range is shown. Dotted line represents recommended screening interval of 12 months

CHAPTER 4: ORAL HPV INFECTION

Prospective Study Of Oral HPV Infections Among Women With And Without Prevalent Cervical HPV Infections

ABSTRACT

Introduction

HPV is linked to both cervical and some oropharyngeal cancers. However, there have been no prospective examinations of the determinants and risk posed by prevalent cervical HPV infections on the incidence of oral HPV infections of the same DNA type. Further, current evidence on the correlation between HPV infections at the two anatomic sites is limited and inconsistent

Methods

Data on 213 women enrolled in the Women's Interagency Health Study cohort who had available data on both oral and cervical HPV infection was utilized. Determinants and risk of incident type-specific oral HPV infections were evaluated using Wei-Lin-Weissfeld models. Multivariate models included cervical HPV infection status, age, alcohol use, condom use during oral sex and recent sex and oral sex history.

Results

Factors associated with an increased risk of incident oral HPV infection included recent history of sexual activity with either a male (adjusted hazard (aHR)=2.47, 95%CI: 1.02-6.01) or female partner (aHR=2.79, 95%CI: 1.14, 6.79) as well as performing oral sex in the prior 6 months (aHR=1.75, 95%CI: 1.16, 2.62). A marginal association was observed for HIV 1.83 (0.94, 3.56) and no association was observed with cervical HPV infection, age, alcohol or condom use during oral sex.

Conclusion

Having a prevalent cervical HPV infection was not associated with an increased risk of acquisition of oral HPV infection; however, sexual activity remains a significant risk factor for acquiring oral HPV infections.

INTRODUCTION

Human Papillomavirus (HPV) infections cause cervical cancer, anal cancer, as well as many oropharyngeal cancers. In the United States, 40-80% of oropharyngeal cancers and over 90% of invasive cervical cancers are associated with HPV [70-72]. However, in spite of this association, currently the relationship between HPV infections at these two independent anatomic sites is not well understood [25]. Further there are unanswered questions about the potential risk and determinants associated with transfer of prevalent infections between the two anatomic sites.

Even though HPV infections are transmitted primarily through sexual contact, it may be possible to transmit infections through non-penetrative sexual contact through means such as either masturbation or autoinoculation [67,68]. Autoinoculation refers to the "transmission of a prevalent HPV infection between the genitals, anal canal, oral cavity or hands of an infected individual during routine genital self-handling" [67,69]. Plausibility for autoinoculation of HPV infections is supported by evidence from a cohort of newly sexually active females where HPV DNA was detected in the fingertips of 30% of women with prevalent cervical infections of at least one HPV type [68]. In this study, the concordance rate between types detected in cervical and fingertip samples was 60% and over 90% of these had the same variants detected in both cervical and fingertip samples [68]. Suggesting that outside of the sexual mode of transmission, transfer of infections between anatomic sites such as the cervix and oropharynx may occur through deposition of infections on the fingertips of individuals with prevalent HPV infections.

Further a cross-sectional examination of the correlation between prevalent oral and cervical HPV infections, comparing women with and without cervical HPV infection,

observed that the prevalence of oral HPV infections among women with cervical HPV infections was significantly higher than among women without any cervical HPV infection (25.5% versus 7.9% p-value= 0.002) [75]. A more recent study using national survey data in the United States, observed a 5-fold increased prevalence of oral HPV infections among women with cervical infections compared to women without any cervical HPV infection [76]. Using data from 10 studies a meta-analysis of the correlation by type between cervical and oral HPV infections reported a pooled prevalence of 18.1% for oral HPV infections among women with a cervical infection [77].

Although these previous studies suggest an increased risk for oral HPV infection among women with a cervical infection, due to their mainly cross-sectional nature [78,75,79] the temporal sequence and risk of oral acquisition of HPV from prevalent cervical infections is presently unknown. Further these previous studies have been severely limited by their sample size and overall the available evidence base on the correlation between cervical and oral HPV infection is inconsistent. Therefore, this study sought to prospectively evaluate the co-factors and risk conferred by prevalent type-specific cervical HPV infections on the subsequent acquisition of the same HPV types orally.

METHODS

Study Design and Population

Data from the Persistent Oral Human Papillomavirus Study (POPS) was utilized for this study. POPS is a prospective cohort study of oral HPV infection nested within the larger Multicenter AIDS Cohort Study (MACS) and Women's Interagency Health Study (WIHS), which are respectively multicenter cohort studies of HIV infection in men and

women. Recruitment into POPS was carried out from October 2009 to October 2011 across multiple sites, using a convenience sample of HIV infected and high-risk HIV negative participants.

Participants in this analysis included a sample of women (N=213) enrolled in POPS between October 2009 and October 2014 at 3 study sites specifically Brooklyn, Bronx and Chicago. These 213 women represented 22.3% of all women in POPS. Other female participants were excluded because they did not have available cervical HPV testing results, within the time period examined. Participants were only included if they had at least one assessment of cervical HPV infection status, either on or after October 2009. In addition, all participants were required to have at least 2 available assessments of their oral HPV infections status, one at entry and the other during follow-up. Entry for this analysis was defined as the first POPS visit where cervical HPV infection status was assessed and after entry participants were followed up regularly at approximately 6-months intervals until the end of follow-up or censoring.

Specimen Collection

Female participants enrolled in POPS are all part of the WIHS cohort where they provide cervical swabs and cervicovaginal lavage samples at each semiannual visit. Many (but not all) of these cervical samples have been tested for cervical HPV, allowing comparison of cervical HPV and oral HPV (assessed) at these study visits. In addition, at each visit participants fill out an interviewer-administered questionnaire, which is used to collect risk factor information on recent behaviors and exposures including sexual practices, alcohol use, smoking, number of sexual partners and sexual orientation.

Assessment of Cervical HPV Infection

The main exposure of interest in this study was type-specific cervical HPV infection and to assess this, cervicovaginal lavage fluid and cervical swab samples provided at entry were tested for the presence of HPV DNA [133]. The HPV types tested for in collected cervical samples, included both oncogenic and non-oncogenic HPV types. Specifically, oncogenic HPV types assessed included: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 and 73 [134,135,133]. The non-oncogenic HPV types assessed included: 6, 11, 26, 42, 53, 54, 61, 62, 64, 66, 67, 69, 70, 71, 72, 81, 82, 83, 84 and 89 [134,135,133].

Assessment of Oral HPV Infection

The primary outcome of interest in this analysis was incidence of type-specific oral HPV infections observed during follow-up. This outcome was assessed using oral rinse samples containing exfoliated epithelial cells provided by each participant after a 30 second gargle, first at the entry visit and at each subsequent six-months follow-up visit [134]. These oral rinse samples were assayed for the presence of HPV DNA associated with the same type-specific HPV infections evaluated and described above under exposure assessment for cervical HPV infection.

For both cervical and oral rinse samples, the HPV DNA types of interest were tested for using amplification with PGMY09/11 polymerase chain reaction primer pools and primers for βglobin [134]. This was then followed by reverse line blot hybridization to the Roche LINEAR ARRAY HPV Genotyping Test (Roche Molecular Systems, Pleasanton, California) [134].

Statistical Analysis

Characteristics of participants in our study were described using median values with associated interquartile range estimates for continuous measures and percentages for categorical variables. A Kaplan Meier plot was used to assess time to incident type-specific oral HPV infection by cervical HPV infection status at entry. Comparing women with and without type-specific infections, the risk and determinants of type-specific oral HPV infections were explored using Wei-Lin-Weissfeld models. The adjusted model included both factors found to be significant in the unadjusted model as well as factors previously identified to be associated with oral HPV infections. Specifically, the adjusted model included age in years on a continuous scale and HIV status defined using a binary, yes or no. In addition, the adjusted model included reported sexual history (no sex, sex with female partner or sex with male partner only), performance of oral sex (yes or no) and condom use during oral sex (yes or no) within the 6 months period prior to each study visit during follow-up. Both the adjusted and unadjusted associations were explored at a significance level of $p \leq 0.05$. All statistical analyses were conducted using STATA 14 [102].

RESULTS

Characteristics of Study Sample

There were 213 women enrolled at the Brooklyn, Bronx and Chicago sites of the POPS and WHIS cohort who had available cervical and oral type-specific HPV data. Median age of participants was 47.5 years (IQR: 41.4-53.2, see Table 4-1) and about 73% of participants were HIV positive. Most (79.3%, see Table 4-1) women were heterosexual

and almost all participants (94.4%) had a history of ever being pregnant. At entry to this substudy (i.e. first study visit in October 2009 or thereafter), 73.0% of women reported recent sexual activity within the prior 6 months and this was primarily (68.3%) with a male partner. In addition, 4.7% (Table 4-1) of women reported recent sex with a female partner with 27% reporting no recent sexual activity. The percentage of women who received oral sex or performed oral sex in the prior 6 months were 30.5% and 28.2% respectively (Table 4-1). Participants were predominantly non-Hispanic Black (66.7%) and most (65.3%) reported an annual income below the federal poverty threshold of $12,060 [136]. Overall, less than half of participants reported alcohol use and this included 16.9% of women who had more than 7 drinks each week (Table 4-1).

Prevalence of exposure and incidence of outcome

Proportion of women with one or more type-specific cervical HPV infections at entry was 12.2% (26). Of the 67 type-specific cervical HPV infections identified at entry, HPV 62 was the most common cervical HPV infection type with a prevalence of 11.9%. Other HPV types common in cervical samples at entry included HPV 53 and 83, which each had a prevalence of 9.0%. Only 9 of the type-specific cervical HPV infections detected at entry correlated by type with HPV infections detected in oral rinse samples for the same individuals at entry and these included infections with HPV types 18, 39, 53, 56, 59, 62 and 83.

In the sample of women enrolled in this study, oral HPV prevalence was higher at study entry than cervical HPV prevalence. About 40% (85/213) of participants had one or more type-specific oral HPV infections, including 152 type-specific oral HPV infections. The most prevalent oral HPV type identified at entry was HPV 16, which was detected in

9.4% (20/213) of women. The second and third most common oral HPV types detected at entry were HPV 62 and 53, which each had a prevalence of 6.1% (n=13) and 4.7% (n=10) respectively.

A total of 969 incident type-specific oral HPV infections were identified and the overall incidence rate of type-specific oral infections during follow-up was 6 per 1000 person-year of follow-up. Further, compared to women without cervical HPV infection, women who had any type-specific cervical HPV infection experienced a higher incidence rate of type-specific oral HPV infections (8.9 vs 9.9 per 1000 person-year of follow-up, Figure 4-1).

Risk factors for incident oral HPV infection

In the unadjusted analysis only HIV infection was significantly associated with the risk of an incident oral HPV infection. All of the other risk factors examined including having a prevalent cervical HPV infection at entry had no significant association in the unadjusted analysis (Table 4-2).

In the adjusted model a recent history of sexual activity and performing oral sex in the prior 6 months were found to be significant. An increased risk of oral HPV infection was observed for women reporting a recent history of sexual activity with either a male (adjusted hazard (aHR)=2.47, 95%CI: 1.02, 6.01) or female partner (aHR=2.79, 95%CI: 1.14, 6.79). In addition, performing oral sex in the prior 6 months was associated with an increased risk (aHR=1.75, 95%CI: 1.16, 2.62). A marginal association was observed for HIV infection (aHR=1.83, 95%CI: 0.94, 3.56) and no association was observed with cervical infection, age, alcohol and condom use during oral sex (Table 4-2).

DISCUSSION

In our assessment of the determinants and risk posed by type-specific cervical HPV infections on the acquisition of incident oral HPV infections of the same type, we observed no significant difference in the risk of oral infections between women with and without one or more type-specific cervical HPV infections at entry. Sexual behavior was a significant predictor of an increased risk of acquiring oral HPV infection, including performing oral sex and a recent history of having sex with either a male or female partner within a recent six months period. As has been reported for males, even among HIV positive and high-risk HIV negative women sexual exposure remains an important route for the transmission of oral HPV infections. The observed association between an increased risk of oral HPV infections and performing oral sex as well as recent sexual activity is consistent with what is currently known about the role of sexual exposures in the etiology of oral HPV infections [137-139].

Data from previous examinations of the contributions of cervical infections to the natural history of oral HPV infections have been inconsistent with some studies reporting either a null association or an increased risk for oral HPV infection among women with a cervical HPV infection. The findings of our study, which is the first prospective examination of the role of prevalent cervical HPV infections in the etiology of oral HPV infections, are consistent with some previous studies that observed no association [140-142]. This absence of an association implies that HPV infections at the two anatomic sites are independent and prevalent cervical infections may play no role in the etiology of oral HPV infections. On the other hand, this lack of an association may also be as a result of the limited number of women who had a prevalent cervical HPV infection at entry.

Similarly, no significant difference in the risk of oral HPV infection was observed for women who used condoms during oral sex and those who did not. Condoms provide a physical barrier, which may protect against HPV infection. However in order to prevent transmission of infections, they have to be consistently and correctly used each time oral sex is performed [143,144]. Therefore, infrequent or inaccurate use may not necessarily protect against infection.

HIV positive individuals compared to HIV negative individuals have been reported to have a 2-3 fold increased risk for acquiring HPV infections [145]. Our study also showed a higher incidence of oral HPV infection among HIV-infected subjects, although the difference was only marginally significant and this is likely due to the limited sample size used. This might also be explained the high prevalence of HAART use among HIV positive participants in this study (Supplemental Table1). HAART use has been shown to mitigate the risk of oral HPV infection among HIV positive individuals [145].

The main strength of our study is its use of a prospective cohort design, which allowed for the temporal sequence of cervical and oral HPV infections to be accurately established. To our knowledge it is the first prospective examination of the role of prevalent cervical infections in the etiology of oral HPV infections. Despite these strengths, our study is limited by the rarity of the main exposure of interest, cervical HPV infection. Only 10% our study sample had one or more cervical HPV infections at entry. Therefore, this may have restricted our ability to detect a difference in the rate of oral HPV infections between women with and without type-specific cervical HPV infections at entry. In addition, the non-random sampling of participants utilized in our study may have resulted in the selection of participants who were not representative or less likely to

have experienced the exposure (given the lower than expected cervical HPV prevalence in this group). Middle-aged women, independent of sexual behavior, are known to have a generally low prevalence of cervical HPV infections [146,147] which could also explain the generally low prevalence of the cervical HPV in our study population.

To conclude data from our prospective cohort study shows that prevalent cervical HPV infections do not increase the risk of incident type-specific oral HPV infections and that HPV infections at these two anatomic sites are independent events. In our study, recent sex with either male or female partners as well as performing oral sex were the only factors associated with an increased risk of oral HPV infections. This provides further evidence that minimizing sexual exposure to HPV may be an effective means of reducing incidence of oral HPV infections.

Table 4-1. Characteristics of 213 Participants at Entry

Characteristic	Overall (N=213) n (%)
Age, years: median (IQR)	47.5 (41.4 - 53.2)
Race	
Black non-Hispanic	142 (66.7)
White non-Hispanic	9 (4.2)
Hispanic, any race	57 (26.8)
Other	5 (2.4)
Center	
Bronx	125 (58.7)
Brooklyn	39 (18.3)
Chicago	49 (23.0)
Sexual Orientation	
Heterosexual	169 (79.3)
Lesbian/Bisexual	42 (19.7)
Unknown	2 (0.9)
Marital Status	
Never Married	47 (22.1)
Married/Living with partner	53 (24.9)
Widowed/Divorced/Separated	51 (23.9)
Other	60 (28.2)
Unknown	2 (0.9)
Ever pregnant	201 (94.4)
Parity	2 (1-4)
Recent sex history	
No sex	57 (27.0)
Sex with female partner	10 (4.7)
Sex with male partner only	144 (68.3)
Received oral sex in the last 6 months	65 (30.5)

Characteristic	Overall (N=213)
	n (%)
Performed oral sex on either a male or female partner in the last 6 months	60 (28.2)
Condom use during oral sex	
Never	45 (21.1)
Always/ Sometimes	15 (7.0)
Not sure/Unknown	153 (71.8)
Income	
≤$6000	44 (20.7)
$6001-$12000	95 (44.6)
>$12000	72 (33.8)
Unknown	2 (0.9)
Alcohol	
Abstainer	116 (54.5)
>0-7 drinks/week	59 (27.7)
>7 drinks/week	36 (16.9)
Unknown	2 (0.9)
Smoking status	
Ever	177 (83.2)
Never	34 (16.0)
Unknown	2 (0.9)
Level of education	
≤Grade 11	98 (46.0)
High school	62 (29.1)
≥College level	50 (23.5)
Unknown	3 (1.4)
HIV positive	155 (72.8)

Table 4-2. Factors associated with incidence of type specific oral HPV infections

Characteristic	Hazard Ratio (95%CI)	Adjusted Hazard Ratio (95%CI)
Any type-specific cervical HPV infection	1.10 (0.74, 1.64)	0.99 (0.67, 1.45)
Age at visit	1.00 (0.98, 1.02)	0.91 (0.70, 1.17)
Recent sex history		
No sex	Ref	Ref
Sex with female partner	1.54 (0.82, 2.88)	**2.79 (1.14, 6.79)**
Sex with male partner only	0.88 (0.62, 1.26)	**2.47 (1.02, 6.01)**
Performed oral sex	1.12 (0.94, 1.33)	**1.75 (1.16, 2.62)**
Condom use during oral sex	1.10 (0.92, 1.31)	1.24 (0.94, 1.64)
Alcohol use		
Abstainer	Ref	Ref
>0-7 drinks/week	0.75 (0.54, 1.04)	0.89 (0.61, 1.30)
>7 drinks/week	0.83 (0.53, 1.31)	0.85 (0.48, 1.52)
HIV positive	**1.97 (1.14, 3.40)**	1.83 (0.94, 3.56)

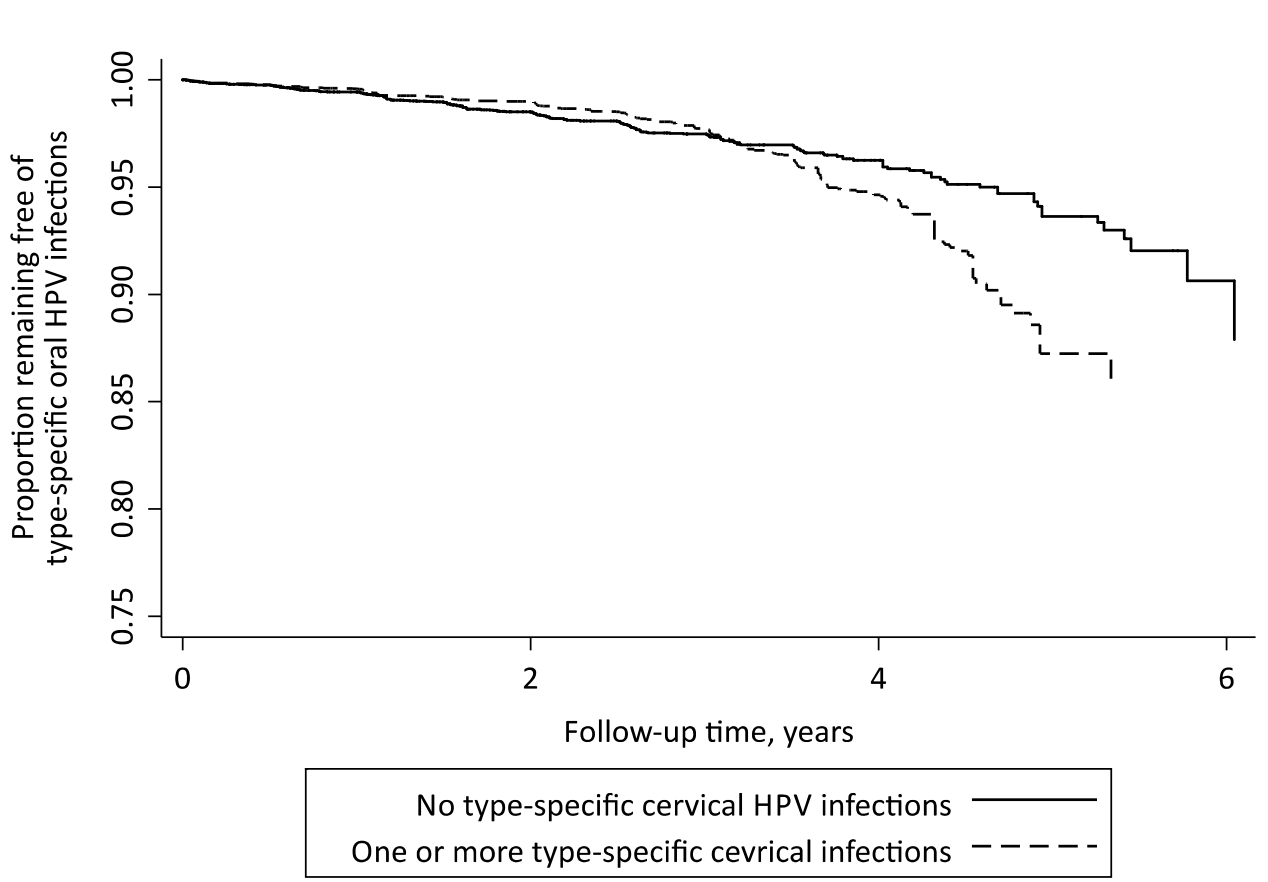

Figure 4-1. Kaplan-Meier survival curve of time to type specific oral HPV infection by HIV status, comparing women with and without cervical HPV infections at entry

CHAPTER 5: SUMMARY OF FINDINGS, IMPLICATIONS FOR PREVENTION AND CONTROL OF INVASIVE CERVICAL CANCER AND FUTURE DIRECTIONS

Utilizing various data sources this research evaluated the prevention and control of ICC among high-risk women within the United States. Specifically, this research assessed the space-time variation in ICC incidence by counties in the state of Maryland. This research also longitudinally assessed trends and determinants of cervical Pap testing among WLWH enrolled in primary care and finally this research evaluated the determinants and risk posed by prevalent type-specific cervical HPV infections on the acquisition of the same HPV types orally. The overarching oral of this thesis research was to generate scientific evidence to facilitate a more targeted approach to addressing the specific needs of the subgroups at highest risk for ICC.

SUMMARY OF MAJOR RESEARCH FINDINGS

In chapter 2 results of our examination of the space-time variation in ICC incidence by counties in the state of Maryland showed most counties had consistently moderate ICC incidence across the 10-year period examined. The average annual age adjusted incidence rate of ICC for Maryland in this time period was 9.7 per 100,000. After further adjusting for county characteristics including percent minority, percent screened for cervical cancer in the last 3-years and median household income, the average annual adjusted statewide ICC incidence rate was 9.2 per 100,000. In the fully adjusted space-time cluster detection analysis several clusters of high and low incidence were detected. These included 3 significant space-time clusters of high and 2 significant space-time clusters of low ICC incidence, most of which were found in fairly recent time periods, between 2009 and 2012. Based on the detected clusters of both high and low ICC incidence we concluded that although rates in some counties have dramatically declined overtime there are some areas in Maryland where ICC still needs to be prioritized and addressed.

In chapter 3 as part of our assessment of the utilization of Pap testing among WLWH we observed that although a large proportion (79%) of women received Pap testing, 21% of women who were in care for 18 months or longer did not receive Pap testing during follow-up at JHH. Further, only 11% of women consistently received Pap testing at the recommended annual interval and some women (5%) were consistently under-screened i.e. they were consistently screened at intervals longer the recommended. WLWH observed to have a decreased likelihood of receiving a Pap test included older women, injection drug users, white women and those who had lived for a longer time with HIV. Only women with a prior abnormal Pap test result were observed to be significantly more likely to receive Pap testing and no association was observed with either CD4 cell count or type of health insurance. Results of our longitudinal examination of Pap testing among WLWH enrolled in care adds to the literature on ICC screening among WLWH and presents potential targets in an urban HIV care setting for closer monitoring and directed interventions to improve utilization.

Finally, in chapter 4 we prospectively evaluated the determinants and risk conferred by prevalent type-specific cervical HPV infections on the subsequent acquisition of the same HPV types orally. Results of our evaluation indicate that women with a recent history of sexual activity with either a male or female partner as well as those who performed oral sex in the prior 6 months had an increased risk of developing incident type-specific oral HPV infections. A marginal association was observed for HIV and no association was observed with cervical HPV infection, age, alcohol or condom use during oral sex. Therefore, these results suggest that having a prevalent cervical HPV infection is not associated with an increased risk of acquiring the same HPV types orally. However,

based on the strong association observed for women with a recent history of sexual activity we concluded that sexual activity remains an important risk factor for acquiring oral HPV infections.

IMPLICATIONS FOR ADDRESSING ICC AND FUTURE DIRECTIONS

Spatial Epidemiology

Our assessment of the space-time variation in ICC incidence directly addresses goal 2 objective 4 of the ICC specific target in the state cancer control plan for Maryland [91]. Our findings indicate that even in recent periods the burden of ICC in Maryland in an uneven, there are significant clusters of high and low incidence rates. Clusters of lower than expected rates identified provide evidence supporting the impact of state and local efforts to address ICC. While the clusters of higher than expected rates suggest that in spite of the progress made over time, some counties have seen an increased ICC incidence rate. These findings can aid the state to prioritize and efficiently address ICC associated morbidity within the state through further investigations and the delivery of targeted interventions to clusters of high rates.

This evaluation of a space-time variation in ICC incidence was conducted at the county level and as such could not explore potential heterogeneity in incidence rates that may be present at smaller geographic units such as at the census tract level within each county [112,51]. Future studies using smaller geographic units of aggregation are needed to better characterize the specific hot and cold spots of ICC incidence within Maryland. In addition, building upon the ecologic study design utilized in this research, further studies

of variation in ICC incidence can employ multilevel models in their assessment. Multilevel modeling would allow an examination of both the independent as well as the combined effects of contextual levels factors, which this research examined and individual level data, which were not incorporated into this analysis [148,149]. Such an approach would adequately model multiple factors at the individual and contextual level that underlie variation in incidence over time [148,150].

ICC Screening Among WLWH

ICC is highly preventable especially if women are consistently and appropriately screened according to guideline recommendations and as the life expectancy for people living with HIV continues to increase it is important that WLWH adhere to screening guidelines in order to mitigate their ICC risk. Results of our longitudinal evaluation of Pap test utilization among WLWH in primary care indicate that for a substantial proportion of WLWH, being engaged in care does not necessarily guarantee routine access to cervical Pap testing as is recommended. Significant determinants of Pap testing for WLWH observed in our study include socio-demographic factors and a prior abnormal Pap test result. These identified factors can be harnessed into interventions that promote adherence to routine Pap testing for WLWH in care. Such interventions may include an educational component that explains the importance of routine screening or may involve the delivery of prompts to either WLWH with the characteristics identified by this research or to their providers at the recommended interval about scheduling the Pap tests.

This assessment of Pap testing among WLWH relied mainly on a comprehensive database of medical and pathology records for WLWH enrolled in primary care at JHH.

Thus, this research could not evaluate variables not routinely captured in medical records including factors such as personal barriers faced by WLWH to routine Pap testing. In order to examine the contribution of such factors to Pap test utilization by WLWH, future studies involving mixed methods approaches of both quantitative methods and qualitative interviews are warranted. Such studies may be illuminating about complex interplay of clinical, sociodemographic factors and personal barriers to routine Pap testing among WLWH [151,152].

The neighborhood in which individuals live has been shown to influence their health care utilization through barriers such as the lack of proximity to a healthcare provider [153-155]. Hence, future studies can also utilize methods of spatial epidemiology to assess if unscreened or underscreened WLWH cluster with specific geographic units. These methods can also be used to examine the role of neighborhood effects in promoting Pap testing among WLWH.

Oral HPV Infection

The strong association observed between sexual exposure and the incidence of type-specific oral HPV infections further underscores the importance of the sexual mode of transmission in the etiology of oral HPV infections. While the lack of an association observed between prevalent type-specific cervical HPV infections and the incidence of oral HPV infections suggests that cervical HPV infections may not play a role in the etiology of oral HPV infections. Thus, in addressing the growing burden of HPV-associated oropharyngeal cancers, it is important that prevention and control programs continue to prioritize and address sexual exposure to HPV infections. Such interventions may include promoting the consistent and correct use of physical barriers such as dental

dams and oral condoms during oral-genital contact in order to minimize exposure to HPV infections orally [156,144,143]. Further; although the HPV vaccine is currently not licensed for the prevention of oropharyngeal cancers, some studies suggest that the vaccine is protective against oral HPV infections [157,158]. Thus, increasing uptake of the HPV vaccine both at the national level and among high-risk groups could potentially decrease the risk of oral HPV infections either directly through primary protection or eventually through herd immunity, once appropriately high vaccination rates have been achieved.

Our study was conducted in a population of HIV positive and high-risk HIV negative women enrolled at three study sites within the United States. Thus, our findings may not reflect the risk of oral HPV infection among women living in regions of the world where HPV prevalence is extremely high. Risk of oral HPV infection in such populations may be significantly higher than that observed for the population studied by this research. Future studies involving women living in high burden regions may further enhance the available evidence about the natural history of oral HPV infections.

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CURRICULUM VITAE

Sally Peprah, B.Pharm (Hons), MSPH, PhD

Personal Data

Ph.D. Candidate, Cancer Epidemiology Track,
Department of Epidemiology,
Johns Hopkins Bloomberg School of Public Health
615 North Wolfe Street, E6039
Baltimore MD 21205
Cell: (516)-965-8668 | email: speprah1@jhu.edu | Skype ID: sallypeprah

Education And Training

2013-2017	**Epidemiology** Johns Hopkins Bloomberg School of Public Health Baltimore, MD	**Ph.D.**
2011-2013	**International Health** Johns Hopkins Bloomberg School of Public Health (JHSPH) Baltimore, MD	**MSPH**
2005 - 2009	**Pharmacy** University of Science and Technology Kumasi, Ghana	**B.Pharm**

Employment

01/2015-present	**Consultant** Center of Hope Phnom Penh, Cambodia
10/2012-05/2014	**Research Assistant** Afro-Cardiac Study, School of Nursing, JHU Baltimore, MD
10/2012-03/2013	**Research Assistant** International Vaccine Access Centre (IVAC) Baltimore, MD
05/2013-09/2013	**Technical Associate**

08/2012-10/2012	**Intern** Management Science for Health (MSH) Arlington, VA
05/2012-12/2012	**Statistical Analyst** Future Health Systems Group Baltimore, MD and New Delhi, India
09/2011-11/2011	**Research Assistant** Department of International Health, JHSPH Baltimore, MD
10/2011-12/2011	**Project Consultant** World Bank Group Washington, DC
02/2011-05/2011	**Contractor**
08/2010-02/2011	**Intern** United States Agency for International Development (USAID) USAID|DELIVER Project Accra, Ghana
08/2009– 06/2010	**Pharmacist, HIV/AIDS Center and Diabetes Clinic** Komfo Anokye Teaching Hospital Kumasi, Ghana

Teaching and Leadership Experience

03/2016- present	**Teaching Assistant, Epidemiologic Inference II** Department of Epidemiology, JHSPH
09/2015-02/2016	**Lead Organizer, World Cancer Day 2016** JHSPH
10/2015-12/2015	**Teaching Assistant, Epidemiologic Inference II** Department of Epidemiology, JHSPH
08/2015-10/2015	**Teaching Assistant, Epidemiologic Inference I** Department of Epidemiology, JHSPH, Baltimore MD
07/2015-08/2015	**Teaching Assistant, Principles of Epidemiology** Department of Epidemiology, JHSPH, Baltimore MD
09/2014-02/2015	**Lead Organizer, World Cancer Day 2015** JHSPH, Baltimore MD
09/2014-10/2014	**Teaching Assistant, Epidemiologic Methods (751)**

Department of Epidemiology, JHSPH, Baltimore MD

09/2013-05/2014 **Coordinator, Pre-doctoral Mentoring Lunch Meetings**
Cancer Epidemiology, Prevention and Control Training Program

08/2009- 05/2010 **Teaching Assistant, Phytochemistry and Plant Morphology**
Faculty of Pharmacy, University of Science and Technology
Kumasi, Ghana

01/2006-05/2008 **Organizer and Co-Host Health Affairs Program**
Focus FM (radio station), University of Science and Technology

08/2007 **Group Leader, Pharmacy Students Rural Outreach Program**
Faculty of Pharmacy, University of Science and Technology
Kumasi, Ghana

09/2003-05/2004 **President Science Club**
Our Lady of Apostles Girls Secondary School
Brong-Ahafo, Ghana

Honors and Awards

08/2013-present **Pre-doctoral Trainee**
Cancer Epidemiology, Prevention and Control Training Grant
Department of Epidemiology, JHSPH, Baltimore MD

10/2013-present **Centre Scholar**
Center to Reduce Cancer Disparities
Sidney Kimmel Cancer Center, JHMI, Baltimore MD

08/2015 -05/2016 **Dr. and Mrs. Roscoe M. Moore, Jr. Scholarship**
Department of Epidemiology, JHSPH, Baltimore MD

2002 **STEM Scholarship**
Ghana Education Service

Professional Associations

Society for Epidemiologic Research (SER)
American Public Health Association (APHA)
Pharmaceutical Society of Ghana

Publications

Sovannara T, Peprah S, Hur C, Tramontano A, Maling E , Hong C.
Estimating The Prevalence of Cervical Abnormalities In HIV-Positive And HIV-Negative Cambodian Women Using Direct Visualization With Acetic Acid: A Cross-sectional Study. Submitted

Posters

04/2016 "Screening For Prevention Of Cervical Cancer In HIV-Positive And HIV-Negative Cambodian Women Using Direct Visualization With Acetic Acid"
8th General Asia Pacific Cancer Leaders Summit 2016, Brisbane, Australia

05/2015 "Invasive Cervical Cancer In High-Risk Women: Infection, Screening and Epidemiology"
Cancer Epidemiology, Prevention and Control Day, JHSPH, Baltimore MD

Research Grant Participation

Student Investigator Maryland Invasive Cervical Cancer Study

Professional Skills

Software: Stata, ArcGIS, R, SPSS, Endnote and Microsoft Office Suite

Languages: English, French and Akan